CYTOGENETIC STUDIES IN CHRONIC MYELOID LEUKÆMIA AND ACUTE LEUKÆMIA ASSOCIATED WITH MONGOLISM

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RECENTLY two preliminary reports have drawn attention to the presence of an abnormal chromosome in a number of cases of chronic myeloid leukæmia (Nowell and Hungerford 1960, Baikie et al. 1960). In both it was noted that, while the chromosome number was normal, there was a morphological abnormality of one of the small acrocentric autosomes, as a result of which this autosome appeared unusually small (fig. 1). In studies of cells cultured from the leucocyte component of the blood, Nowell and Hungerford found this chromosome in five males and two females, while Baikie et al., using the same culture technique, noted it in eight out of twelve patients (three males and five females), all but two of whom had had some form of treatment. Baikie et al. also studied marrow chromosome preparations from ten patients, and found the abnormal chromosome to be present for certain in three of these. The remaining marrow preparations were too poor for an opinion to be expressed on the chromosome content. In 1959 Baikie et al. reported, on the basis of marrow studies, that they could see no abnormality of the karyotype in chronic myeloid leukæmia. But it has become apparent that this failure was related to the appreciably poorer quality of chromosome preparations from bone marrow cells by contrast with those from cells cultured from the blood.

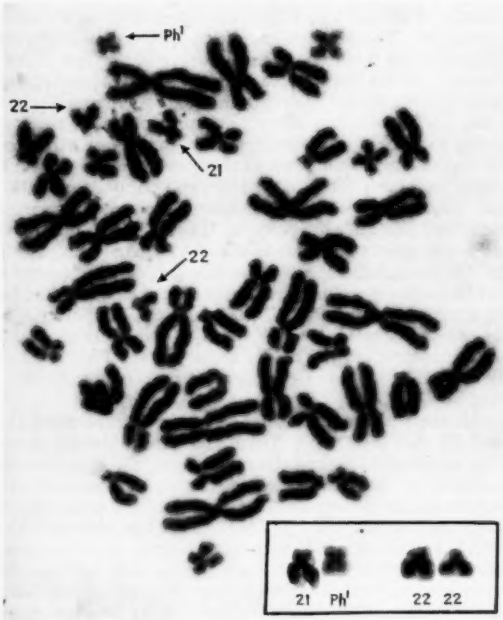

Fig. 1—Cell from case 3.
The 4 acrocentric chromosomes are shown paired up in the inset.

We here report data on the studies of chromosomes, using the blood culture technique, from eighteen patients referred to us with a diagnosis of chronic myeloid leukæmia, three of whom had passed into a phase of acute leukæmia.* We also describe the results of a study, using the same technique, of five cases of acute leukæmia associated with mongolism. These data are reported together with those on chronic myeloid leukæmia as it may be that the chromosome involved in mongolism is the same as that which appears to be abnormal in chronic myeloid leukæmia. In this paper the abnormal chromosome, for the sake of brevity, is referred to by the symbol Ph¹. This is chosen as it indicates the geographical location, Philadelphia in the United States, of the laboratories in which the chromosome was first noted, and thus it accords with the recommendations on the nomenclature of abnormal chromosomes of the Denver conference (*Lancet* 1960).

Technical Considerations

Chromosome studies were made on cells cultured from the leucocyte component of the blood, the culture technique being a modification of that of Moorhead et al. (1960). In most instances the final spreading of the chromosomes was achieved by drying in air. In preparations of this type from subjects without leukæmia and who are not chromosome mosaics, an average of 94% of cells have a count of 46 chromosomes; most of the remaining cells have counts below this mode. The great majority of non-modal cells are thought to arise from the breakage of cells during preparation, with the consequent loss of chromosomes (Court Brown, Jacobs, and Doll 1960). Table I shows that spreading in cases 5 and 16 was caused by squashing the cells between a slide and a coverslip. This technique damages more cells than does that of drying in air, and only about 78% of cells from non-leukæmic individuals have a chromosome count of 46. This is relevant to the findings in case 5, where the proportion of hypodiploid cells was unusually high. Analysis of these cells revealed no constancy of chromosome number or of karyotype, and we conclude that these counts were due to artefacts arising during preparation, and that they are not indicative of a separate cell line.

In cases 6–9 many cells contained gross structural abnormalities of the chromosomes. These included ring chromosomes, dicentric chromosomes, and fragments of chromosome material. In addition the chromosome count distributions were abnormal in one culture from case 6 (on July 4, 1960) and one from case 9 (on July 25). These 4 patients had all been treated by radiotherapy for their leukæmic condition less than 8 weeks before their blood was cultured for the first time, and it has been shown by Tough et al. (1960) that therapeutic irradiation can alter both the chromosome count and chromosome morphology in peripheral blood cells. Consequently we think that, with the exception of the Ph¹ chromosome, the changes noted in these cases were induced by X-ray exposure. This explanation was supported by the findings in further blood cultures in cases 6, 7, and 9, set up respectively about fourteen, twenty-two, and seventeen weeks after the cessation of radiation exposure. In cases 6 and 9 the abnormalities were appreciably less, and in case 7 they were no longer present.

* Eleven of the cases described in this report were also the subject of the report of Baikie et al. (1960).

TABLE I—CHROMOSOME COUNTS IN EIGHTEEN CASES OF CHRONIC MYELOID LEUKÆMIA

—	Case no.	Date (1960)	Spreading technique*	Chromosome counts										Ph¹ present	Ph¹ absent	Ph¹ ?	Remarks
				<43	43	44	45	46	47	48	49	>49	Total				
Untreated cases	1	Sept. 25	A.D.	..	..	..	..	49	1	..	..	..	50	32	13	5	None
	2	„ 30	A.D.	..	..	..	2	34	36	..	..	..	72	16	8	48	Regarded as XY/XXY mosaic. In scorable cells Ph¹ present in 14/17 diploid cells, and in 2/7 hyperdiploid cells
	3	Oct. 18	A.D.	..	..	..	1	26	..	..	..	..	27	24	0	3	None
	4	Nov. 28	A.D.	..	..	3	2	34	..	..	..	..	39	8	11	20	„
		Dec. 19	A.D.	1	2	..	..	22	..	..	..	..	25	18	2	5	„
Treated cases	5	April 5	Sq.	8	..	..	1	17	..	..	..	..	26	20	0	6	None
	6	July 4	A.D.	..	2	3	17	57	..	..	..	..	79	15	12	52	Radiation damage—48 cells
		Aug. 19	A.D.	..	..	..	2	47	1	..	..	..	50	39	3	8	„ „ —6 cells
	7	July 11	A.D.	1	..	3	2	25	..	..	..	2	33	2	10	21	„ „ —15 cells
		Nov. 14	A.D.	..	..	1	1	23	1	..	..	..	26	14	1	11	No obvious radiation damage
	8	July 25	A.D.	..	..	..	..	10	..	..	..	..	10	1	3	6	Radiation damage—2 cells
	9	„	A.D.	..	..	4	12	29	2	1	..	..	48	2	21	25	„ „ —24 cells
		Oct. 24	A.D.	1	2	1	2	32	1	..	..	..	39	4	24	11	„ „ —8 cells
	10	Sept. 5	A.D.	1	1	..	2	46	..	..	..	..	50	49	1	0	None
	11	„ 23	A.D.	..	..	..	1	47	2	..	..	..	50	0	47	3	„
	12	Oct. 10	A.D.	..	..	..	1	48	1	..	..	..	50	11	30	9	„
	13	Nov. 11	A.D.	..	..	3	..	25	..	..	..	..	28	21	0	7	„
	14	„ 18	A.D.	..	..	..	2	48	..	..	..	..	50	0	47	3	„
	15	Dec. 16	A.D.	..	..	..	2	29	..	..	..	..	31	0	30	1	„
Treated cases with acute leukæmia	16	Feb. 3	Sq.	..	..	1	2	32	1	..	..	..	36	0	6	30	None
	17	Aug. 26	A.D.	1	..	2	8	62	5	2	17	..	97	50	13	34	In scorable cells Ph¹ present in 31/43 diploid cells, and in all cells with 49 chromosomes
		Sept. 19	A.D.	1	..	..	1	30	1	1	17	..	51	28	6	17	In scorable cells Ph¹ present in 11/17 diploid cells, and in all cells with 49 chromosomes
	18	„ 16	A.D.	..	..	..	5	44	1	..	..	..	50	0	34	16	None

* A.D. = air drying. Sq. = squashing.

The Ph¹ chromosome is an abnormally small acrocentric chromosome, and is one of the 4 small acrocentric chromosomes of which there are two pairs, numbered 21 and 22 in the Denver classification. The small acrocentric chromosomes from cells from some of the patients reported in this paper are shown in fig. 2. Before a cell could be assessed for the presence or absence of the Ph¹ chromosome, it was necessary to identify as a group all the small acrocentric chromosomes, which in the male includes the Y chromosome. The assessment was then only made provided that all these chromosomes appeared well fixed and well spread in the preparations. If these criteria were not satisfied, no decision was taken regarding the presence or absence of the Ph¹ chromosome. Reference will be made to the number of cells in which the chromosome was either definitely seen or from which it was definitely absent. It will be appreciated, nevertheless, that had it been possible to score every cell, the proportion of cells showing the Ph¹ chromosome might have been different.

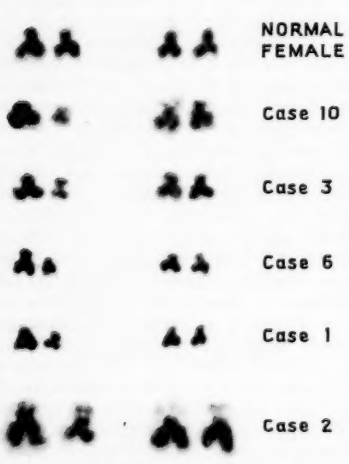

Fig. 2—Chromosome pairs 21 and 22 in 5 cases of chronic myeloid leukæmia.

The chromosomes from case 2 are shown in greater enlargement to demonstrate the satellites.

In preparations showing obvious radiation damage, a decision could only be made on a smaller proportion of cells than in other preparations, because, apart from the question of spreading and fixation, the radiation damage itself often precluded a decision being made.

Results

Chronic Myeloid Leukæmia

The distributions of the chromosome counts are given in table I, and the relevant clinical and haematological data are summarised in table II. The Ph¹ chromosome was seen in all four untreated cases, in eight of eleven treated cases, and in one of three cases examined after they had passed into a phase of acute leukæmia.

Among the untreated cases the chromosome count distributions were of a normal pattern for cases 1, 3, and 4. In these the Ph¹ chromosome was noted in 32 out of 50, 24 out of 24, and 26 out of 39 cells in which a decision could be made. The findings in case 2, however, are more complex. As well as the features of chronic myeloid leukæmia, this patient also showed features of Klinefelter's syndrome. Moreover sex chromatin studies on cells from the buccal smear were positive, a sex chromatin body being seen in about 40% of the cells. Analysis of the cells with 47 chromosomes revealed a karyotype consistent with an XXY chromosomal sex, while those with a count of 46 had a karyotype consistent with an XY chromosomal sex. The findings, therefore, were compatible with the patient being a chromosome mosaic of the type XY/XXY. A study of the chromosomes from a skin culture, however, showed evidence for one stem-line only, containing 47 chromosomes. This finding is not incompatible with the patient being a mosaic, for in our experience the degree of admixture of the different stem-lines in mosaics may vary greatly from tissue to tissue (Jacobs et al. 1960, and unpublished data). In the blood culture both stem-lines contained a proportion of cells with the Ph¹ chromosome. Table I shows that, of those cells that could be scored, 14 out of 17 diploid cells, and 2 out of 7 hyperdiploid cells, were so affected. These findings were confirmed by blood culture set up after the patient had begun treatment with busulphan, the respective proportions being 11 out of 13, and 5 out of 8 cells. 50 cells were studied from a skin culture and in none of these was the Ph¹ chromosome noted. The possible significance of the findings in this case will be discussed.

All the patients in the treated group, except cases 11, 13, and 15, had been given X-ray treatment, although in case 9 this treatment followed chemotherapy. Of these irradiated patients all had been exposed either to localised splenic irradiation or to wide-field irradiation of the abdomen, using medium-kilovoltage X rays. No attempt has been made to give details of the tissue radiation doses, because in the treatment of chronic myeloid leukæmia each patient may be regarded as unique in respect of the total dose effective in producing an adequate fall of the white cell count. It has been noted already that cases 6–9 showed evidence of gross chromosome damage which is considered to be the result of recent X-ray treatment.

TABLE II—HÆMATOLOGICAL AND TREATMENT DATA IN EIGHTEEN CASES OF CHRONIC MYELOID LEUKÆMIA

Case no.	Sex	Age (yr.)	Date of diagnosis	Hæmatological data at time of diagnosis *	Details of treatment †	Date of chromosome studies (1960)	Hæmatological data at time of chromosome studies *
1	M	38	March, 1959	Hb 8·1; W.B.C. 42,000 (N. 32%, Bd. 14%, Bas. 11%, Eos. 12%, My. 23%, Bl. 1%, Ly. 6%, Mon. 1%); Pl. 1, 100,000	None	Sept. 25	W.B.C. 40,000 (N. 37%, Bd. 18%, Eos. 8%, My. 16%, Mmy. 8%, Bl. 13%)
2	M	59	Sept., 1960	Hb 9·1; W.B.C. 235,000 (N. 35%, Bd. 16%, My. 36%, Mmy. 12%, Bl. 1%); Pl. 119,000	None	Sept. 30	As before
3	F	66	Oct., 1960	Hb 10·5; W.B.C. 205,000 (N. 33%, Bas. 8%, Eos. 5%, My. 30%, Bl. 17%, Ly. 3%, Mon. 4%); Pl. 561,000	None	Oct. 18	As before
4	M	53	April, 1960	Hb 9·0; W.B.C. 20,000 (My. 50%); Pl. 140,000	None	Nov. 28 Dec. 22	Hb 8·8; W.B.C. 93,000 (N. 32%, Bd. 10%, My. 48%, Bl. 7%, Ly. 3%); Pl. 260,000 Hb 9·6; W.B.C. 42,000 (N. 38%, My. 51%, Ly. 6%, Mon. 5%). Pl. 231,000
5	F	36	Oct., 1958	Hb 11; W.B.C. 385,000 (N. 4%, Bd. 43%, Bas. 4%, Eos. 3%, My. 10%, Mmy. 25%, Bl. 9%, Ly. 2%); Pl. 270,000	X: Oct. 27–Nov. 12, 1958 X: May 20–July 6, 1959	April 5	W.B.C. 292,000 (N. 42%, Bas. 8%, Eos. 3%, My. 33%, Bl. 13%, Ly. 1%)
6	F	67	April, 1958	Hb 12·7; W.B.C. 190,000 (N. 4%, Bd. 47%, Bas. 13%, Eos. 5%, My. 4%, Mmy. 19%, Bl. 2%, Ly. 2%, Mon. 4%); Pl. 240,000	X: May 21–June 4, 1958 X: July 30–Aug. 13, 1959 X: April 27–May 12, 1960	July 4 Aug. 19	W.B.C. 31,000 (N. 51%, Bas. 3%, My. 31%, Bl. 5%, Ly. 9%, Mon. 1%) W.B.C. 84,000 (N. 44%, Bas. 9%, Eos. 1%, My. 35%, Bl. 10%, Mon. 1%)
7	F	58	June, 1959	Hb 8·7; W.B.C. 170,000 (N. 35%, Eos. 2%, My. 31%, Ly. 30%, Mon. 2%); Pl. 570,000	X: July 7–21, 1959 X: June 2–14, 1960	July 11 Nov. 14	W.B.C. 5000 (N. 60%, Bd. 18%, Bas. 3%, My. 12%, Ly. 4%, Mon. 3%) W.B.C. 103,000 (N. 57%, Bd. 11%, Bas. 4%, Eos. 1%, My. 15%, Bl. 11%, Ly. 1%)
8	F	57	May, 1960	Hb 7·7; W.B.C. 296,000 (N. 40%, Bd. 8%, Eos. 2%, My. 29%, Mmy. 18%, Ly. 3%); Pl. 85,000	X: May 31–July 7, 1960	July 25	W.B.C. 5000 (N. 84%, My. 2%, Ly. 7%, Mon. 7%)
9	F	62	Dec., 1958	W.B.C. 53,000; no other data available; blood and marrow films consistent with chronic myeloid leukæmia	B: April–June, 1959 X: July 21–Aug. 14, 1959 X: May 24–June 24, 1960	July 25 Oct. 24	W.B.C. 2000 (N. 74%, Bas. 1%, Ly. 15%, Mon. 10%) W.B.C. 26,000 (N. 76%, Eos. 1%, My. 12%, Bl. 2%, Ly. 5%, Mon. 4%)
10	F	63	July, 1958	Hb 11·6; W.B.C. 22,000 (N. 48%, Eos. 3%, My. 22%, Ly. 27%); Pl. 397,000	X: Nov. 17–Dec. 5, 1958 X: Dec. 4–22, 1959	Sept. 5	W.B.C. 136,000 (N. 40%, Bas. 14%, Eos. 8%, My. 29%, Bl. 6%, Ly. 3%)
11	M	45	Aug., 1957	W.B.C. 80,000 (N. 77%, My. 6%, Mmy. 8%, Bl. 4%)	B: Oct., 1958–Oct., 1959	Sept. 23	Hb 15·0; W.B.C. 17,000 (N. 64%, Bas. 2%, Eos. 1%, My. 13%, Ly. 20%); Pl. 200,000
12	M	66	Sept., 1959	Hb 9·8; W.B.C. 145,000 (N. 70%, Bas. 4%, My. 22%, Ly. 2%, Mon. 2%); Pl. 130,000	X: Oct. 15–Nov. 5, 1959	Oct. 10	W.B.C. 131,000 (N. 43%, Bd. 10%, Bas. 2%, Eos. 3%, My. 23% Mmy. 19%)
13	F	14	Oct., 1960	Hb 5·3; W.B.C. 790,000; films consistent with diagnosis of chronic myeloid leukæmia	B: Nov. 2, 1960—	Nov. 11	W.B.C. 710,000
14	F	54	Aug., 1956	Hb 13·8; W.B.C. 40,000 (N. 16%, Bd. 47%, Bas. 8%, Eos. 3%, My. 4%, Mmy. 8%, Ly. 11%, Mon. 3%)	X: June 25–July 19, 1957 X: March 25–April 7, 1960	Nov. 18	Hb 13·2; W.B.C. 39,000 (N. 79%, My. 16%, Ly. 3%, Mon. 2%) Pl. 102,000
15	M	41	April, 1956	Hb 9·2; W.B.C. 30,000 (N. 73%, Bas. 1%, Eos. 4%, My. 5%, Mmy. 2%, Bl. 1%, Ly. 10%, Mon. 4%)	B: July 18–Aug. 25, 1960	Dec. 16	Hb 12·8; W.B.C. 7000 (N. 70%, Bd. 12%, Bas. 2%, Eos. 1%, Ly. 10%, Mon. 5%); marrow films compatible with chronic myeloid leukæmia
16	M	71	Oct., 1958	Diagnosis of chronic myeloid leukæmia in October, 1958, no details available. On July 22, 1959, Hb 9·8; W.B.C. 178,000 (N. 51%, Bas. 3%, Eos. 5%, My. 34%, Bl. 5%, Ly. 2%); Pl. 512,000	X: July 30–Aug. 20, 1959 X: Jan. 29–Feb. 10, 1960	Feb. 3	W.B.C. 86,000 (N. 20%, Bas. 1%, Eos. 2%, My. 4%, Bl. 68%, Ly. 5%)
17	F	62	Sept., 1959	Hb 9·7; W.B.C. 206,000 (N. 33%, Bas. 1%, My. 50%, Bl. 8%, Ly. 2%, Mon. 1%)	X: Sept. 28–Oct. 19, 1959 X: March 31–April 8, 1960 M: Aug. 29, 1960—	Aug. 26 Sept. 19	Hb 8·6; W.B.C. 54,000 (N. 55%, My. 10%, Bl. 31%, Ly. 4%); Pl. 254,000 Hb 10·9; W.B.C. 17,000 (N. 82%, My. 6%, Bl. 6%, Ly. 6%); Pl. 263,000
18	M	22	Sept., 1958	Hb 11·0; W.B.C. 286,000 (N. 7%, Bd. 60%, Bas. 1%, Eos. 2%, My. 11%, Mmy. 9%, Bl. 4%, Ly. 3%, Mon. 3%); Pl. 265,000	X: Sept. 29–Oct. 22, 1958 X: March 25–28, 1960 X: Aug. 9–15, 1960 P: May 3–Sept. 16, 1960	Sept. 16	W.B.C. 147,000 (N. 5%, Bl. 64%, smear-cells 31%)

* Hb = hæmoglobin (g. per 100 ml.). W.B.C. = white blood cells (per c.mm.). Pl. = platelets (per c.mm.).
† X = X-rays.
N. = neutrophils. Bd. = band forms. Bas. = basophils.
B = busulphan.
Eos. = eosinophils. My. = myelocytes. Mmy. = metamyelocytes.
P = prednisolone.
Bl. = blast-cells. Ly. = lymphocytes. Mon. = monocytes.
M = 6-mercaptopurine.

TABLE III—CHROMOSOME COUNTS IN FIVE CASES OF ACUTE LEUKÆMIA ASSOCIATED WITH MONGOLISM

Case no.	Date (1960)	Chromosome counts				
		45	46	47	48	Total
1	June 28	1	2	35	..	38
2	July 1	..	1	33	..	34
3	July 13	1	2	36	2	41
4	July 26	..	..	33	2	35
5	Oct. 31	..	..	30	..	30

All cases except no. 2 were untreated, and in each spreading was by air drying.

Reference will be made later to a possibly important difference between this group of cases, in respect of the frequency of the Ph¹ chromosome, as compared with the frequency in the untreated cases and those treated but not showing radiation damage. Among the treated patients, three cases (11, 14, and 15) stand apart in that the Ph¹ chromosome was not definitely noted in any cell, and these will be discussed in some detail.

The Ph¹ chromosome was noted in only one of three patients (case 17) who had entered an acute leukæmic phase, and this particular case will be discussed.

Studies of the chromosomes in cells from skin cultures have been made in cases 1, 2, and 10. The Ph¹ chromosome was not found in any of these preparations.

Acute Leukæmia in Mongols

The chromosome count distributions are given in table III for four untreated cases and one treated case of acute leukæmia in mongols, and the relevant clinical and hæmatological data are summarised in table IV. The treated patient (case 2, table IV) was in remission. The count distributions show no significant difference from those of non-leukæmic mongols who demonstrate the classical cytogenetic feature of mongolism—namely, trisomy of autosome 21 (Denver classification). There is, therefore, no evidence from the results presented in table III that these cases of acute leukæmia are associated with any other chromosome abnormality.

Discussion

The Ph¹ chromosome has been found in twelve out of fifteen patients diagnosed as having chronic myeloid leukæmia, and in one of three patients who had passed from the chronic leukæmic state into that of acute leukæmia. Nowell and Hungerford (1960), in a preliminary report, found the chromosome in seven patients ranging from untreated cases to those in a phase of acute leukæmia. Altogether, therefore, the Ph¹ chromosome has been found in twenty patients with chronic myeloid leukæmia ranging from untreated cases to those in the terminal stages of the disease.

Five examples of acute leukæmia in mongols have been studied, and in none of these was any chromosome abnormality found other than that associated with mongolism. In the following discussion particular attention will be paid to: (1) the frequency of the Ph¹ chromosome; (2) the interpretation of the findings in a patient with sex chromosome mosaicism and chronic myeloid leukæmia (case 2); (3) the cases of chronic myeloid leukæmia not showing the Ph¹ chromosome (cases, 11, 14, and 15); (4) the findings in three patients in an acute leukæmic phase (cases 16–18); (5) the nature of the Ph¹ chromosome; (6) the association of leukæmia and mongolism; and (7) the possibility that the same chromosome is involved both in mongolism and chronic myeloid leukæmia.

Frequency of the Ph¹ Chromosome

In most cases showing the Ph¹ chromosome, there were cells in which it was clearly not found. It is generally understood that in cultures from non-leukæmic individuals the mature cells of the myeloid series do not divide, and the dividing cells are probably monocytes and large lymphocytes, or cells closely resembling them. We have not so far seen the Ph¹ chromosome in subjects without chronic myeloid leukæmia, and as it is closely linked to this type of leukæmia, we conclude that the cells with this chromosome are leukæmic cells. It follows, therefore, that in blood cultures from such leukæmic individuals, myeloid cells (presumably the immature forms) can be stimulated to divide. As non-myeloid cells will also divide it is understandable that the Ph¹ chromosome is usually only seen in a proportion of cells.

To compare the frequency of the chromosome in different groups of patients, the numbers of cells in which the chromosome was present have been related to the total numbers of cells in which a decision could be reached as to its presence or absence. At the same time the cases in which the chromosome was not found (11, 14, and 15), and also the cases in an acute leukæmic phase (16–18) have been excluded. Among the untreated patients 98 out of 132 cells showed the Ph¹ chromosome (74·2%), and among the treated patients 178 out of 283 cells contained the chromosome (62·9%). The reduction in the proportion of cells with the chromosome in the treated group is due to its appreciably lower frequency in those patients showing chromosome damage due to radiation. All six cultures showing radiation damage were from patients who had completed a course of treatment not less than 2 weeks and not more than 17 weeks previously. In this group only 63 out of 136 cells showed the Ph¹ chromosome (46·3%), whereas in the rest of the treated group the chromosome was present in 115 out of 147 cells (78·2%). Of the treated patients not showing radiation damage, case 13 was a girl who had started treatment with

TABLE IV—HÆMATOLOGICAL AND TREATMENT DATA IN FIVE CASES OF ACUTE LEUKÆMIA ASSOCIATED WITH MONGOLISM

Case no.	Sex	Age (yr.)	Date of diagnosis (1960)	Hæmatological data at the time of diagnosis *	Details of treatment †	Date of chromosome studies (1960)	Hæmatological data at the time of chromosome studies *
1	F	3	May	Hb 8·3; W.B.C. 60,000 (Ly. 92%, many abnormal)	None	June 28	Hb 5·2; W.B.C. 19,000 (90% blasts and smear-cells); Pl. 38,000
2	M	7	March	Hb 4·9; W.B.C. 60,000 (almost all cells were blasts)	P: March 15–April 6, 1960 M: March 21, 1960—	July 1	Hb 13·2; W.B.C. 2500 (no certain leukæmic cells seen)
3	F	24	June	Hb 7·3; W.B.C. 40,000 (Bl. 80%); Pl. 30,000	None	July 13	Hb 5·7; W.B.C. 29,000 (82% leukæmic cells); Pl. 18,000
4	F	5	July	Hb 9·4; W.B.C. 5000 (N. 6%, Bd. 19%, Bl. 23%, Ly. 52%); Pl. 75,000	None	July 26	As before
5	F	5	October	W.B.C. 3000 (N. 17%, My. 6%, Bl. 54%, Ly. 23%)	None	Oct. 30	As before

* † For abbreviations see table II.

busulphan only 9 days before the chromosome studies. In cases 5, 7 (the count of Nov. 14), 10, and 12 the most recent X-ray exposure had been 21 weeks before the chromosome study.

The difference in frequency of the Ph¹ chromosome between those cases showing radiation damage and the other treated cases is significant ($X^2=30{\cdot}82$, $P<0{\cdot}001$). One explanation might be that the cells carrying the Ph¹ chromosome were more sensitive to the radiation-induced damage than were cells with a normal chromosome complement, but other explanations can be advanced.

Findings in Case 2

Case 2 represents a special problem in interpretation since the blood chromosome studies suggested that the patient was a sex chromosome mosaic of the XY/XXY type, while analysis of the cells from skin culture showed only cells of the XXY type. This latter finding does not invalidate a diagnosis of mosaicism as it has already been pointed out that the degree of admixture of cells may vary between tissues. It might be argued, however, that the true constitution of the patient was of cells with an XXY sex chromosome complement, and that the diploid line of cells was a subline of leukæmic cells derived from an original line of hyperdiploid leukæmic cells. But if this was the case, it would be reasonable to expect all the diploid cells to contain the Ph¹ chromosome. This was not so; therefore we assumed that the patient was a sex chromosome mosaic.

The patient may have been conceived as a normal XY zygote and then developed an XXY stem-line; or, conversely, he may have been conceived as an XXY zygote and developed an XY stem-line. The finding of only a proportion of Ph¹ cells in either stem-line indicates that the appearance of the chromosome must have postdated the origin of the two stem-lines, and at least two hypotheses might explain the limited frequency of the chromosome in either stem-line:

The first hypothesis is that some event occurred at least twice, once in each stem-line, causing the production of two sublines each containing the Ph¹ chromosome. Also the damage leading to the formation of the Ph¹ chromosome could be due to intrinsic factors, or could be caused by some agent external to the chromosome.

The second hypothesis postulates that the abnormal chromosome arose in one cell in either the XY or the XXY stem-line. Later a further divisional error involved a cell carrying the Ph¹ chromosome, which caused the production of a cell with the sex chromosome complement of the other stem-line. On this second hypothesis it can be argued that cells arising on the basis of one or more divisional errors may be unduly prone to the occurrence of a further error.

Cases Not Showing the Ph¹ Chromosome

The Ph¹ chromosome was not found in three treated patients who had no evidence of an acute leukæmic transformation:

CASE 11.—There is a high probability that the leukæmia was radiation-induced. The patient had ankylosing spondylitis, and between 1946 and 1950 he had six courses of X-ray treatment. Except for one course to the right elbow joint, all were given to the spine and/or sacroiliac joints. In August, 1957, the patient had (on routine examination) a white cell count of 80,000 per c.mm., and a diagnosis of chronic myeloid leukæmia was made on the appearance of the blood film. Neither the spleen nor liver was enlarged, and in view of the patient's good general health, treatment was not considered necessary. By October, 1958, the spleen had become palpable and the white cell count was 110,000 per c.mm. (myelocytes 50%); intermittent treatment with busulphan was given for a year, the aim being to keep the white cell count below 20,000 per c.mm. When chromosome studies were done on Sept. 23, 1960, he was still in satisfactory remission. This case appears atypical in respect of the slight enlargement of the spleen and the relatively long remission after treatment with busulphan, as well as in the history of radiation exposure.

CASE 14.—The diagnosis of chronic myeloid leukæmia was established in August, 1956, when the spleen was enlarged to the level of the umbilicus. The patient's general health was good, and no treatment was thought necessary. By June, 1957, the spleen had enlarged further and the white cell count had risen to 104,000 per c.mm. (myelocytes 23%). Localised splenic irradiation was given from June 25 until July 19, and then a second course was given in 1960 from March 25 until April 7. The patient was last seen on Nov. 18, in apparently good general health, although her spleen extended down into the left iliac fossa, and the white cell count was 39,000 per c.mm. As with case 11, the course has been relatively benign.

CASE 15 is yet another example of a patient with a previous history of radiotherapy for ankylosing spondylitis, who does not show the Ph¹ chromosome. The patient was given X-ray treatment to the spine and sacroiliac joints in 1955 from Feb. 17 until April 26; at that time his white cell count was 10,000 per c.mm. and the differential count was normal. Chronic myeloid leukæmia was diagnosed in April, 1956, some 14 months after the X-ray treatment. Experience from the survivors in Hiroshima and Nagasaki, and also irradiated spondylitics, indicates that after a single heavy exposure the latent period usually lies between 4 and 8 years, the increased frequency of leukæmia not being noted until the 2nd post-exposure year. It seems unlikely, therefore, that X-ray treatment induced leukæmia in this patient, but the possibility cannot be definitely excluded. When leukæmia was diagnosed in 1956 the patient's general health was good, and no treatment was thought necessary. He was kept under observation, and between 1956 and 1959 his white cell count varied from 30,000 to 96,000 per c.mm. The spleen became palpable for the first time in July, 1960, at which time the white cell count was 19,600 per c.mm. Treatment with busulphan was begun on July 18 and stopped on Aug. 25. When seen on Dec. 16 for blood chromosome studies, his general health was fair, and the spleen was not palpable. In this case the disease has run a relatively benign course, and the splenomegaly has been slight.

These three cases in which the Ph¹ chromosome has not been found have in common an unusually long history after diagnosis, and all three have so far run a relatively benign course. No more can be done at this stage than to draw attention to the possible correlation between the negative cytogenetic findings and the clinical behaviour of the disease. But further studies may show that a distinct sub-group of cases of chronic myeloid leukæmia can be differentiated on these grounds.

Findings in the Phase of Acute Leukæmia

In both cases 16 and 18 chromosome studies were only made after the development of an acute leukæmic phase, characterised respectively by 68% and 64% of the white cells being primitive blast cells.

The negative findings in these two cases must be contrasted with the positive findings in case 17, a patient in an early stage of an acute transformation in whom two distinct cell lines were present—one with 46 and the other with 49 chromosomes. In the diploid line the Ph¹ chromosome was present in 42 out of 60 scorable cells, while all 34 scorable cells in the hyperdiploid line contained the chromosome. Furthermore, there was a constant karyotype in all cells with 49 chromosomes, the 3 additional chromosomes being made up of a medium submetacentric, a small metacentric, and a small acrocentric chromosome. In the hyperdiploid line all the cells contained the Ph¹ chromosome, which strongly indicates

that it was derived from a cell or cells in the diploid line containing the same chromosome.

The clinical histories of all three cases were fairly typical of chronic myeloid luekæmia. The results from the other typical cases reported here suggest that the great majority of such cases are associated with a Ph¹ chromosome and a normal chromosome count distribution. It is a reasonable assumption, therefore, that the Ph¹ chromosome might have been found in cases 16 and 18 if they had been studied before the acute leukæmic phase. It is also reasonable to presume that, under similar circumstances, no abnormal count distribution would have been found in case 17; and that the hyperdiploid line with 49 chromosomes is associated with the acute transformation of the disease. The failure to detect an abnormality in cases 16 and 18 cannot at present be explained.

Nature of the Ph¹ Chromosome

So far no attention has been paid to the nature of the Ph¹ chromosome, but it must be derived from one of the small acrocentric chromosomes (nos. 21 and 22, Denver classification); the appearance of the Ph¹ chromosome suggests that it is formed as a result of the loss of chromosome material from the long arm of one of these chromosomes. No abnormality has been seen in any other chromosome. Two explanations could account for the Ph¹ chromosome: firstly, a deletion may have occurred; or, secondly, the appearance could be the result of a translocation involving a small acrocentric chromosome with another. It is not feasible on the present evidence to distinguish between these two possibilities, because the amount of material involved in such a translocation would not make an appreciable difference to the appearance of many of the other chromosomes in the set. The fact that in three cases examination of the chromosomes in cells from skin cultures showed no abnormality, whereas the Ph¹ chromosome was found in cells from blood cultures, indicates that the abnormality has arisen de novo in the hæmopoietic system, presumably in the myeloid series of cells. The question of which of the two pairs of small acrocentric chromosomes is more likely to be involved in chronic myeloid leukæmia will be considered later.

Association of Leukæmia and Mongolism

Data are presented on the distribution of the chromosome counts in blood culture studies from five cases of acute leukæmia associated with mongolism. Contrary to our experience with many cases of acute leukæmia in adults or in children who are not mongols, we find that the cells in cultures of the blood from leukæmic mongols divide abundantly, in this respect resembling the cultures of non-leukæmic blood. The data show no evidence of chromosome abnormalities associated with the leukæmic state, but the possibility remains that in all instances the leukæmic cells did not divide in culture. Unfortunately there is no way of determining what cells do divide, but it seems reasonable to assume that a proportion of the metaphase cells studied were leukæmic. On this assumption, therefore, present evidence does not suggest that acute leukæmia in mongols is associated with any chromosome abnormality apart from that of the mongol karyotype.

Attention has been drawn to the association between leukæmia and mongolism; perhaps the most important evidence was provided by Stewart et al. (1958). In a study of 677 out of 792 childhood deaths from leukæmia notified to the Registrar General during 1953–1955, they found that leukæmia was associated with mongolism in eighteen cases (2·6%). The frequency of mongolism at birth is of the order of 1/600 (0·17%). Assuming that all such mongols survive, then it appears that the incidence of mongolism in a group of children developing leukæmia is about fifteen times as great as in a group of children selected at random from the national population. But the mortality among mongol children is very high in the early years of life by comparison with that of normal children, and if this differential mortality were to be taken into account, the liability of mongols to develop leukæmia may be appreciably greater than that indicated above.

An abnormality of polymorphonuclear lobulation has been described in mongols (Mittwoch 1958), and it is reasonable to presume that both this and the increased disposition toward leukæmia are linked with the chromosome abnormality in mongolism, which is trisomy or effective trisomy for a small acrocentric autosome.

Concluding Comment

Finally attention should be drawn to the following points:

1. On present evidence the majority of cases of chronic myeloid leukæmia are associated with the Ph¹ chromosome.
2. The Ph¹ chromosome is an abnormal small acrocentric chromosome (either no. 21 or 22, Denver classification) formed as a result of either a deletion or a translocation.
3. Mongols are either trisomic, or effectively trisomic, for a small acrocentric chromosome, believed to be no. 21.
4. Mongolism is associated with an increased disposition towards the development of acute leukæmia.
5. There is so far no evidence for a chromosome abnormality in acute leukæmia in mongols, other than that associated with mongolism.

For purposes of argument it may be postulated that a locus exists on the chromosome involved in mongolism which in some way is concerned with leucopoiesis, and it will be assumed that this chromosome is no. 21. If the postulate is extended to include the suggestion that the same chromosome is involved in chronic myeloid leukæmia as in mongolism, then two conclusions follow: firstly, triplication of the locus is associated with an increased liability towards acute leukæmia; and, secondly, either a deletion or a translocation involving the locus is associated with most cases of chronic myeloid leukæmia.

We would emphasise, however, that the above remarks constitute no more than a working hypothesis and only more extensive investigation can prove its validity. But there can be no doubt of the potential value of cytogenetic studies in improving our understanding of the nature of leukæmia.

Summary

Data are reported on chromosome studies of blood cultures from eighteen cases of chronic myeloid leukæmia, three of which had developed acute leukæmia. In thirteen of these an unusually small acrocentric chromosome was found, which has been designated the Ph¹ chromosome. Among the cases reported is one of sex chromosome mosaicism of the XY/XXY type, and one in an acute leukæmic phase with a second stem-line of cells characterised by a chromosome count of 49.

The five cases in which the Ph¹ chromosome was not found comprise three patients in whom the disease has pursued an unusually benign course, and two patients in the terminal stages of a phase of acute leukæmia.

There is evidence that the chromosome appears significantly less often in blood cultures from patients with

radiation chromosome damage after X-ray treatment of the leukæmia.

Negative cytogenetic findings in respect of the leukæmia are presented for five cases of acute leukæmia associated with mongolism.

It is postulated that the same chromosome is involved in chronic myeloid leukæmia as in mongolism—presumed to be no. 21 (Denver classification). The Ph[1] chromosome appears to have resulted from either a deletion or a translocation involving this chromosome, which may carry on it a genetic locus concerned with leucopoiesis.

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PROTEIN-LOSING ENTEROPATHY

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IN so-called idiopathic hypoproteinæmia—a syndrome of hypoproteinæmia with œdema, but without proteinuria and with normal hepatic function—an abnormal gastrointestinal protein loss has been demonstrated in every case where it has been searched for (Gordon 1959, Gordon et al. 1959, Schwartz and Jarnum 1959). In two such cases displaying an abnormal radiological picture of the small intestine, but no signs of malabsorption, laparotomy findings have been reported (Schwartz and Jarnum 1959). A diffuse lesion was found in the small intestine: the wall was thickened and on the serosal surface dilated lymphatics were visible. The dark brown colour of the intestine was remarkable. Histological examination showed a normal mucosa and a heavy infiltration of the muscular coat with brown granules.

In the present paper we report a case of this syndrome, in which additional information concerning serum-protein degradation and turnover was obtained by studying albumin transport into the pleural and abdominal cavities, and by immunoelectrophoresis of pleural, intestinal, and ascitic fluids. We also describe the histological findings in the intestinal wall, liver, and skeletal muscle.

Case-report

A woman, aged 49, was admitted to the Aarhus Kommunehospital on Sept. 15, 1959.

Since 1944 she had noticed intermittent swelling of both feet and legs. The tendency to œdema gradually increased, and from 1953 onwards, her legs had been constantly swollen. Sometimes, the abdomen, breasts, and hands would also swell. She had been treated with digitalis, diuretics, and plasma transfusions without effect. Otherwise she had enjoyed good health, and she had never had gastrointestinal complaints.

Both legs appeared equally thickened and heavy, as if chronic lymphœdema was present. Superimposed pitting œdema could be demonstrated on both feet and legs, and occasionally on the thighs. Above the inguinal ligaments she appeared entirely normal. Examination of heart, lungs, and abdomen showed nothing abnormal. The liver was not enlarged, and there were no signs of ascites.

Investigations

Total serum-protein was permanently decreased to 4·0–4·8 g. per 100 ml. The hypoproteinæmia was mainly due to a reduction of serum albumin, which ranged between 40 and 50% of total protein, as determined by paper electrophoresis. Low values were also found for γ-globulin, ranging from 10 to 15% of total serum-protein. Serum-cholesterol was 163 mg. per 100 ml.

The urine did not contain protein, and results of kidney-function and liver-function tests were normal. Electrocardiograms and X-rays of heart and lungs were likewise normal. Serum-calcium was 8·9 mg. per 100 ml.; other serum-electrolytes within normal limits.

Examination of gastric secretion, after stimulation with histamine, showed achlorhydria. The stools appeared normal; the fat content at a single analysis was 10 g. per day. The glucose-tolerance test was normal. Xylose test: 6·4 g. excreted in 5 hours (normal). X-rays of the stomach, small intestine, and colon showed no abnormalities.

Investigations with polyvinylpyrrolidone labelled with ^{131}I (^{131}I-P.V.P.) and turnover studies with ^{131}I-labelled human serum-albumin (^{131}I-albumin) were consistent with a protein-losing enteropathy. Repeated X-rays of the small intestine in January and again in March, 1960, now revealed an abnormal patchy segmentation of the barium meal in a seemingly limited part of the ileum. At this time X-rays of the chest also showed accumulation of fluid in both pleural spaces. Owing to the possibility of a localised intestinal lesion, a laparotomy was decided upon.

Operation

Laparotomy was carried out on March 30. The peritoneal fluid appeared milky and was slightly increased in quantity. The proximal 1·5 m. of the jejunum was thickened, congested, and œdematous. Numerous small brownish pigmentations were scattered over the entire intestinal surface. The small blood-vessels were dilated, but more conspicuous were the numerous dilated lymphatics, which were seen not only on the intestinal wall, but also on the corresponding part of the mesentery. The latter was carefully examined, but found to contain only a few lymph-nodes of normal size. The liver appeared normal. The intestinal lesion was not sharply defined, but subsided gradually about halfway down the intestine, except for the dilated lymphatics, which extended even further. In view of the length of the affected part of jejunum, resection was considered unjustified.

Histology

A biopsy specimen was taken from the intestine, including all layers and almost the whole circumference of the wall. A lymph-node was removed from the mesentery, and a biopsy specimen was taken from the liver during the operation. Later, biopsy material was taken from the right gluteal muscle.

The intestinal mucosa was normal. In the submucosa, a few phagocytes were found containing a yellowish-brown pigment,

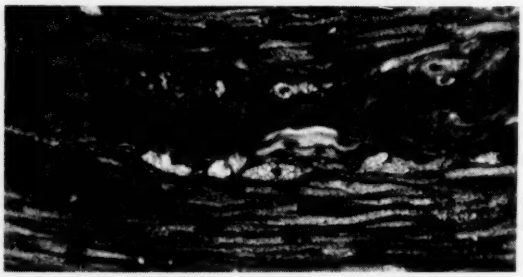

Fig. 1—Fluorescent pigment deposits in external muscular layer of jejunum. Longitudinal section. ×400.

and the lymphatic vessels were slightly dilated. The most remarkable findings were in both layers of the external muscular coat, which contained large quantities of yellowish-brown pigment in the muscle-cells as well as in numerous phagocytes between the muscle bundles. The pigment stained black with Sudan black B, it was acid-fast and positive to periodic-acid/Schiff. Examination of unstained sections by fluorescence microscopy showed that the pigment deposits fluoresced with a yellow light (figs. 1 and 2). Staining reactions for iron were negative.

The liver-cells contained pigment with similar characteristics to that in the intestinal wall, but otherwise appeared normal. Bile pigments were not present (fig. 3). The mesenteric lymph-node showed a normal structure and no pigment could be detected. In skeletal muscle pigment deposits were present in the muscle-cells. They were fluorescent and showed the same staining properties as the pigment in intestinal muscle and liver.

Special Investigations

^{131}I-P.V.P. test.—The cumulative fæcal output of the tracer was determined over a 5-day period after intravenous injection

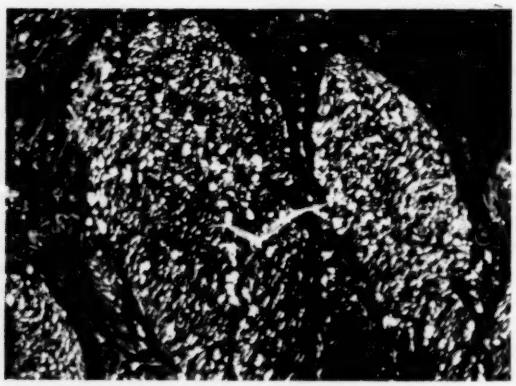

Fig. 2—Fluorescent pigment deposits in external muscular layer of jejunum. Cross section. ×200.

of ^{131}I-P.V.P. (Gordon 1959). The average molecular size of the polymer is about 40,000. In normal persons and in patients without diseases affecting the serum-protein pattern or gastrointestinal function, less than 1% of the amount injected will appear in the fæces.

^{131}I-albumin metabolism.—^{131}I-albumin was prepared according to the method of Veall et al. (1955). 98–99·5% of the activity in the final preparation was protein-bound.

^{131}I-albumin was given twice: (1) to obtain data on albumin metabolism, and (2) in order to study albumin transport into the pleural cavity and into the abdominal cavity during laparotomy. On the latter occasion ^{131}I-albumin was injected intravenously at the moment the peritoneum was opened. Activity was measured in peritoneal fluid and in washings of surgical swabs and covers. Pleural fluid was withdrawn and analysed almost daily for 12 days after the injection of ^{131}I-albumin.

The plasma-disappearance curve was drawn from the activity of daily plasma samples (over a period of almost 3 weeks), which were counted in a well-type scintillation counter, connected to a Tracerlab 'Superscaler'. Radioactivity was measured in homogenised fæces and 24-hour urinary samples. Calculation of albumin degradation was made according to the methods of Pearson et al. (1958) (urinary ^{131}I-output as a percentage of daily mean contents of ^{131}I-albumin in plasma) and Matthews (1957) (mathematical analysis of the plasma-disappearance curve of ^{131}I-albumin).

Serum-protein concentration was determined by Kjeldahl analysis, applying the factor 6·25 for calculating protein from nitrogen concentration. Serum-albumin concentration was

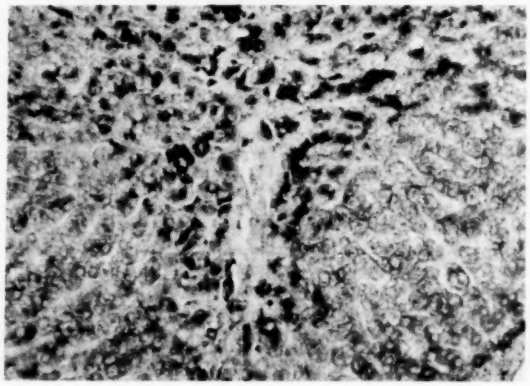

Fig. 3—Pigment deposits in the liver stained with Sudan black B. ×125.

obtained from serum-protein and paper electrophoresis according to Laurell et al. (1956).

Immunoelectrophoresis of serum, ascitic fluid, and intestinal juice was performed by Dr. Jørgen Clausen, department of biochemistry, University of Copenhagen.

Results

^{131}I-P.V.P. test.—The cumulative 5-day fæcal output after intravenous injection was 5·9% of the injected dose (normal value, less than 1%). This demonstrates an abnormally high gastrointestinal permeability for substances of high molecular weight.

Albumin metabolism.—The results of a ^{131}I-albumin-degradation study, carried out 2 months before the operation are given in table I. It appears that the albumin turnover in terms of quantity (0·204 g. per kg. per day) was normal, while the amount of circulating albumin (0·78 g. per kg.) was less than half of the normal value. As the extravascular pool constituted a normal fraction of the total albumin pool, it follows that this was much reduced. This small size of pool was due to a greatly increased degradation-rate, which by either method was almost 3 times higher than the normal average.

TABLE I—DATA ON ^{131}I-ALBUMIN METABOLISM

—	Patient	Normal values
Weight	64·0	...
Serum albumin (g. per 100 ml.)	1·88	3·8–5·1
Circulating albumin (g. per kg.)	0·78	1·3–3·0
Albumin degradation, percentage of circulating albumin per day	26·2* } 28·4† }	6–14
Albumin turnover (g. per kg. per day)	0·204	0·13–0·28
Extravascular albumin pool, percentage of total albumin	61	48–69

Degradation-rate calculated according to the methods of Pearson et al. (1958)* and Matthews (1957)†. Normal values are from Jarnum and Schwartz (1960b).

TABLE II—PROTEIN AND TOTAL LIPID CONTENT IN SERUM AND EXTRAVASCULAR FLUIDS

—	Total protein (g. per 100 ml.)	Albumin		Total lipid (mg. per 100 ml.)
		g. per 100 ml.	Percentage of total	
Serum	4·42	2·25	51	534
Ascitic fluid ..	2·52	1·36	54	432
Pleural fluid ..	1·37	0·73	53	102

Fæcal ^{131}I-excretion.—The cumulative excretion of ^{131}I after intravenous injection of ^{131}I-albumin was 2·01% of the injected dose in 5 days as compared with a normal figure of less than 0·3% (Jarnum and Schwartz 1960b). Daily fæcal ^{131}I-output made up about 4% of total ^{131}I-excretion as compared with 0·6% in normal subjects (Steinfeld et al. 1960). The non-dialysable fraction of ^{131}I in fæces during the 5-day period ranged from 40 to 66% of total fæcal activity.

Extravascular Fluids

Ascitic fluid was obtained during laparotomy. The total lipid concentration was 432 mg. per 100 ml., as compared with 534 mg. in serum and 102 mg. per 100 ml. in pleural fluid. The protein concentration in ascitic fluid was 1·73 g. per 100 ml., increasing to 2·52 g. per 100 ml. in a second sample, collected 45 minutes later during laparotomy. Paper electrophoresis gave albumin concentrations of 0·9 and 1·4 g. per 100 ml. respectively (corrected for trailing).

Immunoelectrophoresis revealed the presence of several proteins: large amounts of albumin, α-1-3-5-S-glycoprotein, α-1-serum-mucoid, 2 unidentified α-1-globulin., α-1-cæruloplasmin, α-1-haptoglobin, α-2-lipoprotein, α-2-macroglobulin, β-1-A-transferrin, β-2-A-globulin and γ-globulin. A partial enzymatic breakdown of proteins had occurred as indicated by uneven precipitation arcs.

Intestinal fluid.—No visible fluid was present after enterotomy. Only a small sample (less than 0·5 ml.) of jejunal fluid could be obtained by aspiration through long catheters, which were rinsed with saline. Part of the diluted intestinal fluid was immediately added to soybean trypsin inhibitor,* 20 mg. per 10 ml. Another part was added to an equal volume of 10% trichloroacetic acid and centrifuged. Non-protein-bound activity was determined in the supernatant. In the sample withdrawn 40 minutes after injection of ^{131}I-albumin, 72% of the radioactivity was protein-bound.

Paper electrophoresis showed a trace of albumin, but quantitative estimation was not possible owing to the inaccuracy of the method in this low concentration range.

Immunoelectrophoresis showed appreciable amounts of albumin, Schultze's α-1-3-5-S-glycoprotein, probably traces of transferrin, and considerable amounts of γ-globulin.

Pleural fluid.—Samples were withdrawn immediately after the operation and almost daily during the succeeding 12 days. The albumin content varied between 0·7 and 1·0 g. per 100 ml. These determinations were made after concentration by ultrafiltration. The pleural fluid was never milky. Immunoelectrophoresis showed the presence of albumin, transferrin, and γ-globulin.

* Soybean trypsin inhibitor was supplied by Novo, Copenhagen.

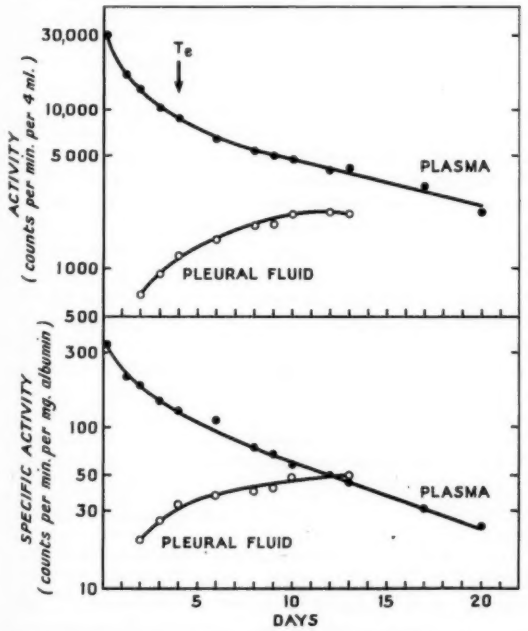

Fig. 4—Radioactivity in plasma and pleural fluid after intravenous injection of ^{131}I-albumin during laparotomy.

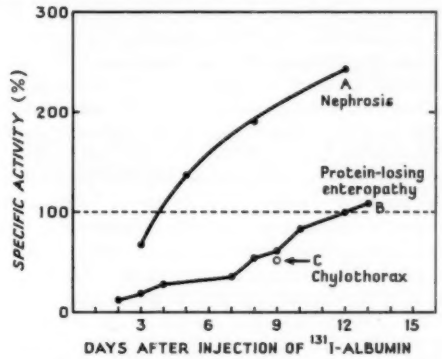

Fig. 5—Specific activity of pleural fluid related to plasma specific activity in nephrosis (A), protein-losing enteropathy (B), and gastric carcinoma complicated by chylothorax (C).

^{131}I-albumin in Ascitic and Pleural Fluids

Ascitic fluid.—The two samples of ascitic fluid, withdrawn 20 and 65 minutes after the injection of ^{131}I-albumin, had a specific activity that was 1·3% and 59% of the specific activity in plasma. Thus a rapid exchange with intravascular activity seemed to take place in the peritoneal fluid. This process was also illustrated in another way. In washings of surgical swabs and covers applied to the peritoneal cavity and abdominal content, the amount of protein and ^{131}I-albumin recovered was considerably higher than could be accounted for from the concurrent blood loss. Details of these and similar investigations in other patients will be published elsewhere. In the present patient the " extra " plasma protein loss, in excess of plasma-protein derived from hæmorrhage, proceeded with a rate equal to more than half of the total circulating plasma-protein per 24 hours, regardless of the method of calculation employed (^{131}I-albumin or total protein as determined by Kjeldahl analysis).

Pleural fluid.—The total amount of extravascular activity at equilibrium time (T_e) was 61 and 59% of the activity remaining in the body at the first and second ^{131}I-albumin studies. This suggests a fairly constant albumin distribution. In calculating the extravascular pool from these figures, the assumption is made that the total specific activity in the extravascular compartment is equal to that of plasma at T_e. At the second degradation study the extravascular activity in pleural fluid was followed over a 12-day period. The result is given in fig. 4. The pleural specific activity did not reach that of plasma until 12 days after the injection. Consequently the specific activity in other extravascular compartments must have exceeded that of plasma at the theoretical T_e (in the present patient, 3·9 days after the injection of ^{131}I-albumin).

One would expect that T_e would be short in diseases accompanied by a rapid albumin turnover, and that the specific

activity in effusions would soon equal that of plasma. In fig. 5 comparative data on pleural and plasma specific activity are given in three patients—namely, the present patient, a patient with nephrotic syndrome, and a patient with chylothorax. The nephrotic patient had bilateral pleural effusions, probably slight ascites, and œdema of the legs. He had an extremely high albumin degradation-rate (47·6% of circulating albumin per day). His pleural fluid specific activity exceeded that of plasma within about 4 days, whereas it took 12 days in the present case of protein-losing enteropathy. In a third patient (C, fig. 5) with gastric carcinoma causing right-sided chylothorax, and with a degradation-rate of 11·5% per day, it took more than 9 days. The curves demonstrate that at no time does true equilibrium exist throughout the extravascular compartments.

Discussion

Our patient had permanent hypoproteinæmia due to abnormal intestinal loss of protein, as indicated by increased excretion of ^{131}I-P.V.P., increased turnover rate of labelled serum-albumin, and increased fæcal excretion of ^{131}I following intravenous injection of ^{131}I-albumin.

It is now well established that several diseases may be associated with hypoproteinæmia due to abnormal gastrointestinal protein loss, such as intestinal lymphogranulomatosis (Jarnum and Schwartz 1960b), gastric cancer (Birke et al. 1959, Jarnum and Schwartz 1960a), hypertrophic gastritis (Citrin et al. 1957, Schwartz and Jarnum 1959), regional enteritis (Steinfeld et al. 1960, Vesin et al. 1960a), ulcerative colitis (Steinfeld et al. 1960), and malabsorption with steatorrhœa (Schwartz and Jarnum 1959, Vesin et al. 1960b, Young et al. 1959). In these patients the loss of serum-protein into the digestive tract is explained by exudation at the site of the lesion, since in some of these cases it has been possible to prevent the protein loss and thereby to correct hypoproteinæmia by surgical resection of the anatomical lesion.

In addition to these conditions, there remains a different category of protein-losing enteropathy to which our patient belongs. Several patients in this group have been subjected to laparotomy, which has revealed a diffuse intestinal lesion involving large segments of the small intestine. The intestinal wall has been found to be thickened by œdema and congestion. In two cases, Schwartz and Jarnum (1959) reported the presence of brown pigmentation scattered over large areas of the intestinal wall, which by microscopic examination was found to consist of granules in the external muscular coat. In the present patient a similar pigmentation was found, and large deposits of the brown-yellow pigment could be demonstrated inside the muscle-cells and in phagocytes in the external muscle layer. Furthermore, similar pigment accumulations were found in liver-cells and in scant amounts in skeletal muscle.

The chemical nature and significance of this pigment remains obscure. Histochemically it has the characteristics of lipo-pigments, to which a number of different terms have been applied—e.g., lipofuscin, hæmofuscin, or ceroid, all believed to be derived from lipid precursors. Several years ago Pappenheimer and Victor (1946) described a similar pigment, called ceroid, in four patients, of whom two evidently were cases of idiopathic hypoproteinæmia. Of the remaining two, one had a gastrocolic fistula, chronic diarrhœa, hypoproteinæmia, and œdema; and one had nontropical sprue without hypoproteinæmia. In these cases pigment was abundant in the external muscular coat of the lower œsophagus, stomach, and small intestine. Outside the alimentary canal, pigment was found in several other tissues, including the liver, skeletal muscle, myocardium, and kidney. Pappenheimer and Victor (1946) also found ceroid in a few cases of liver cirrhosis, one case of cœliac disease, and one of cystic fibrosis of the pancreas. In the recently described syndrome of chronic idiopathic jaundice, a pigment is found in the liver, with properties similar to that in our patient: it was sudanophilic, argentophilic, positive to periodic-acid/Schiff, and fluoresced under ultraviolet light (Dubin 1958).

Experimentally, similar fluorescent pigments can be produced in skeletal muscle and in the central nervous system of vitamin-E deficient animals (Einarson and Telford 1960). Prompted by this observation, our patient was tentatively given tocopherol acetate, 200 mg. per day for four weeks, without benefit, however.

The presence of pigment in other disorders and its widespread occurrence outside the digestive tract suggests that these deposits represent a secondary or concomitant phenomenon, rather than a causative lesion in relation to the intestinal protein loss.

In all patients with gastrointestinal protein loss, the hypoproteinæmia is due mainly to a low serum-albumin level, but in most cases a low or subnormal γ-globulin content is also found. In the present case γ-globulin ranged between 0·4 and 0·8 g. per 100 ml., which is below normal. Low γ-globulin concentrations were also found in all but one of a series of nineteen patients studied by Gordon and Waldmann (1959). The quantitative aspects of a possible intestinal leakage of γ-globulin have not been studied so far. Recently Holman et al. (1959) demonstrated γ-globulin and other serum-proteins in intestinal fluids from patients with intestinal protein loss as well as in normal subjects. These findings suggest that gastrointestinal protein loss represents a quantitative rather than a qualitative abnormality.

The intestinal drain on serum-albumin is associated with an increased turnover rate of albumin. The rate of synthesis and of degradation in terms of percentage of circulating or total albumin is increased, but because of the considerably reduced albumin pool, the absolute amount of albumin catabolised per day is within normal limits. The term hypercatabolic hypoproteinæmia is based on the occurrence of an increased turnover-rate secondary to increased degradation-rate.

In this disorder, sites of abnormal protein loss other than the alimentary canal have not yet been demonstrated. As indicated by the results concerning albumin transport across the pleural membranes, no accelerated albumin degradation took place in this compartment. In pleural fluid ^{131}I-albumin concentration increased slowly and did not reach that of plasma in terms of specific activity until 12 days after the injection, as against a period of 4 days in a patient with nephrotic syndrome and an albumin degradation rate two and a half times as high. In neither patient was a true equilibrium between plasma and pleural fluid obtained. From this it appears that the so-called equilibrium time used for pool calculation by Pearson et al. (1958) is not a point where equilibrium is present throughout the extravascular compartments but only—as these authors mention—a point where the net transfer of the labelled substance into and out of the extravascular compartments is identical.

The dilatation of the intestinal lymphatics and the presence of milky ascitic fluid, possibly originating from intestinal lymph, might indicate an affection of the intestinal lymphatic apparatus. This was also suggested by Gordon and Waldmann (1959), who in a review of the literature found that dilated lymphatics were noted in all

of seven patients with idiopathic hypoproteinæmia who had undergone laparotomy. In three of their own patients, spontaneous chylous effusions occurred. The general frequency of this finding cannot be assessed, however, as often it can only be demonstrated during laparotomy.

In the present case a high specific activity arose rapidly in ascitic fluid. Similarly, it was found that a considerable amount of plasma protein traversed the peritoneal membrane as estimated from the amount of protein recovered from elutions of surgical swabs and covers. An abnormal migration across the peritoneal membrane is further indicated by the presence of the chylous effusion containing increased amounts of fat, albumin, and several other serum proteins, which had been subjected to a partial enzymatic breakdown.

Our findings are consistent with the concept of an abnormal escape of lymph into the lumen of the gut and into the peritoneal cavity, due to an increased pressure in lymphatic vessels in the intestinal wall and mesentery. This concept does not necessarily imply an obstructive lesion in the efferent lymphatic pathways. Observations on transperitoneal protein migration in this and in other patient categories suggest (Jarnum 1961) that protein-losing enteropathy presumably is associated with a much increased intestinal lymph-flow, which by itself could account for the presence of dilated lymphatics.

Summary

A case of protein-losing enteropathy is presented. The patient, a woman of 49, had hypoproteinæmia due to low serum-albumin and low γ-globulin, œdema, pleural effusions, and an abnormal radiological picture of the small intestine, but no dyspeptic symptoms. Her albumin turnover-rate was increased. An abnormal fæcal output of ^{131}I was demonstrated after intravenous injection of ^{131}I-albumin and ^{131}I-polyvinylpyrrolidone.

Laparotomy showed a diffuse intestinal lesion involving a large part of the jejunum, which was congested, œdematous, and contained large quantities of a brown pigment in the external muscular coat. The pigment was acid-fast, sudanophilic, positive to periodic-acid/Schiff and fluorescent. Similar pigment deposits were found in the liver and in skeletal muscle, although in smaller amounts.

Studies were carried out of the transfer of intravascular ^{131}I-albumin to the pleural and peritoneal cavities. Specific activity in pleural fluid did not equal that of plasma until 12 days after injection of ^{131}I-albumin, while specific activity and protein content in ascitic fluid suggested a rapid exchange with intravascular albumin.

Immunoelectrophoresis of intestinal and ascitic fluids revealed several plasma proteins in both.

The findings suggest that hypoproteinæmia in protein-losing enteropathy is due to an abnormal transfer of plasma protein into the intestinal lumen, as well as into the peritoneal cavity, across both surfaces of the gut.

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SERUM FATTY-ACID PATTERNS IN CORONARY-ARTERY DISEASE

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IN recent years considerable attention has been paid to the possible interrelation of dietary fats, blood-lipids, and atherosclerosis. By means of silicic-acid chromatography and gas/liquid chromatography the blood lipids can now be separated into three major components—the cholesterol esters, triglycerides, and phospholipids—and the fatty-acid patterns in each of these fractions can be determined in detail. In this paper we report a study of the fatty-acid patterns of these fractions in a group of patients suffering from coronary-artery disease; and we compare the results with those of a group of sixteen apparently normal subjects previously studied (Lawrie et al. 1961).

Material and Methods

Sera from sixteen male and two female patients were analysed. The ages of the patients range from 47 to 77 years, with an average of 58. Fourteen had unequivocal evidence of previous myocardial infarction. The remainder had clinical and electrocardiographic evidence of myocardial ischæmia. Fourteen were receiving anticoagulant therapy with 'Dindevan' (phenindione). Sixteen were outpatients on an unrestricted diet, and two were inpatients receiving an ordinary ward diet. 20 ml. of venous blood was withdrawn from each patient before breakfast.

The methods of analysis used are similar to those described by us in a previous study (Lawrie et al. 1961). In brief: lipid was extracted from the serum and the acetone-soluble fraction

TABLE I—THE FATTY-ACID COMPOSITION OF SERUM LIPIDS IN FASTING SUBJECTS WITH CORONARY-ARTERY DISEASE. (Figures for each component refer to its mean and standard deviation expressed as a percentage by weight of the total fatty acids in each fraction.)

Acid	Cholesterol esters (17)	Triglycerides (14)	Phospholipids (14)
12 : 0	Tr.	0·7±0·6	Tr.
12 : 1	Tr.	Tr.	—
13 : 0	Tr.	Tr.	—
14 branched	—	0·6±0·8	—
14 : 0	1·7±1·0	3·1±1·6	1·1±0·4
14 : 1	0·8±0·7	1·9±1·1	Tr.
15 : 0	0·6±0·4	1·1±0·8	0·6±0·5
Unknown	Tr.	0·5±0·5	Tr.
16 : 0	14·9±4·2	20·2±6·0	25·1±5·2
16 : 1	5·7±2·1	7·5±3·2	4·1±1·9
17 : 0	0·5±0·4	0·8±0·6	0·9±0·7
Unknown	Tr.	0·6±0·7	0·8±0·5
18 : 0	2·9±1·5	4·3±1·6	11·3±3·1
18 : 1	19·9±4·9	26·4±9·9	17·9±4·1
18 : 2	30·3±10·8	10·3±3·3	19·6±5·0
18 : 3	2·9±8·8	1·5±1·7	0·6±0·9
19 : 0	0	0	0
Uknown	0·7±0·9	0·6±0·8	—
20 : 0	1·6±1·8	3·5±6·1	1·2±1·5
20 : 1	0·5±1·1	2·3±3·2	0·5±0·6
20 : 2	0·5±0·9	0·7±1·2	—
20 : 3	1·4±1·7	2·1±3·2	2·2±1·4
20 : 4	6·4±6·0	3·6±6·1	7·4±2·3
20 : 5	1·4±2·6	1·7±4·9	1·0±2·2
20 unsaturated	5·0±6·4	3·3±3·4	5·6±6·2

"Tr."="Trace amount"=a component present in over half the analyses, but whose mean was under 0·5%. A dash indicates a component present in less than half the analyses and whose mean was under 0·5%.

(containing cholesterol ester and triglyceride) derived from it was applied to a silicic-acid column. Silicic-acid chromatography, slightly modified from the method of Hirsch and Ahrens (1958), was used to separate the cholesterol ester from the triglyceride. The acetone-insoluble fraction of the serum-lipid represented phospholipid. The fatty acids were obtained from each of the fractions, methylated with diazomethane, and submitted to gas/liquid chromatography using a Pye argon-gas chromatograph. The liquid phase was polyethylene glycol adipate at a temperature of 174°C. The acids of chain length from C_{12} to C_{20} inclusive were analysed.

Identification.—Acids were identified by using the relative-retention volume data of Farquhar et al. (1959), and by comparing the times of emergence of unknown acids with those of known acids run under similar chromatographic conditions. Details regarding specific identification of the serum fatty acids have been discussed elsewhere (Lawrie et al. 1961).

Nomenclature.—The nomenclature used to simplify description of the many fatty acids is that introduced by Ahrens et al. (1959). A dual symbol is used; the first figure refers to chain length and the second to the number of double bonds present. A prefix indicates the configuration of the double bonds or the presence of branching, and a suffix denotes their situation. Thus, *cis* 18 : 1^9 refers to oleic acid.

Results

The fatty-acid patterns from C_{12} through C_{20} of the three major lipid fractions from patients with coronary-artery disease are shown in table I. In table II, the major fatty-acid components in each lipid fraction are compared with the corresponding acids derived from the serum of apparently healthy subjects (Lawrie et al. 1961). Each acid is expressed as a percentage by weight of the total fatty acids within each fraction.

Statistical analyses were carried out on the acids to detect any significant differences between those of the normal subjects and those of the patients suffering from coronary-artery disease. Few such differences were found. In the cholesterol-ester fraction there was no significant difference between the groups. In the triglyceride fraction significantly less lauric acid (12 : 0), less of the unknown acid following the 15 : 0 acid, and more of the unknown acid following the 18 : 2 acid were found in the patients with coronary-artery disease. These patients also had more palmitoleic acid (16 : 1) and more of the unknown acid following the 17 : 0 acid in the phospholipid fraction. With the exception of palmitoleic acid, the component acids involved in these differences each represented less than 1% of the total.

Discussion

From a study of tables I and II, two conclusions can be drawn. Firstly, there is considerable variation in the fatty-acid composition of the cholesterol esters, triglycerides, and phospholipids both in the sera of normal controls and in those of patients with coronary-artery disease. Secondly, the fatty-acid patterns of the coronary group closely resemble those of the normal group. All but one of the differences are concerned with certain fatty acids, each of whose concentration is less than 1% of the total, and it would be hazardous to draw any conclusion from these minor differences.

James et al. (1957) using gas/liquid chromatography, studied the fatty-acid patterns of the acetone-soluble fraction (cholesterol ester plus triglyceride) and of the acetone-insoluble fraction (phospholipid) in the plasma of normal persons and in those with coronary-artery disease. They did not find any significant difference between the two groups; but they noted that there was usually slightly more oleic acid in the acetone-soluble fraction of the patients with coronary-artery disease, and suggested that the fatty-acid patterns of cholesterol esters and triglycerides should be determined separately. Our results indicate that there are no significant differences in the oleic-acid content of the cholesterol esters or triglycerides in the two groups.

Sinclair (1956) suggested (1) that the dietary in the more technically-advanced countries was deficient, either absolutely or relatively, in unsaturated fatty acids and might contain unnatural fats as the result of food processing; (2) that these alterations in dietary fat could lead to esterification of the cholesterol of the blood with saturated or unnatural fatty acids; and (3) that the

TABLE II—THE FATTY-ACID COMPOSITION (MAJOR COMPONENTS ONLY) OF THE LIPID FRACTIONS OF SERUM FROM NORMAL INDIVIDUALS, PATIENTS WITH CORONARY ARTERY DISEASE, AND AORTIC ATHEROSCLEROTIC TISSUE (BÖTTCHER ET AL. 1960a). (Figures for each component refer to its mean value and standard deviation (when available) expressed as a percentage by weight of the total fatty acids in each fraction.)

Acid	Cholesterol esters			Triglycerides			Phospholipids		
	Normal group (15)	Coronary group (17)	Aortic tissue (6)	Normal group (13)	Coronary group (14)	Aortic tissue (6)	Normal group (13)	Coronary group (14)	Aortic tissue (6)
14 : 0	1·5±0·7	1·7±1·0	1·4	3·8±1·7	3·1±1·6	3·4	1·2±0·8	1·1±0·4	1·0
16 : 0	13·8±4·0	14·9±4·2	13·7	21·0±6·2	20·2±6·0	21·6	26·7±7·3	25·1±5·2	38·8
16 : 1	6·0±2·0	5·7±2·1	5·7	7·3±2·5	7·5±3·2	6·1	2·4±1·2	4·1±1·9	1·2
18 : 0	3·3±1·9	2·9±1·5	1·9	3·7±2·2	4·3±1·6	7·3	10·3±3·4	11·3±3·1	19·3
18 : 1	21·7±6·3	19·9±4·9	28·3	26·0±11·3	26·4±9·9	40·1	16·7±3·6	17·9±4·1	12·8
18 : 2	35·2±13·0	30·3±10·8	37·0	11·9±6·0	10·3±3·3	10·8	17·2±5·0	19·6±5·0	5·1
20 : 3	2·6±4·0	1·4±1·7	2·2	0·8±2·1	2·1±3·2	0·6	2·6±2·6	2·2±1·4	2·2
20 : 4	3·8±3·4	5·4±6·0	5·1	3·4±4·3	3·6±6·1	2·9	6·2±3·0	7·4±2·3	12·3

abnormal esters so formed might play some part in causing atherosclerosis. He also suggested that similar changes in the fatty-acid composition of the blood-phospholipid could increase blood coagulability and so dispose to coronary-artery thrombosis.

It is not possible to argue conclusively, from the present data, either for or against this hypothesis. Firstly, there is the difficulty of obtaining an adequate control group. This applies especially to coronary-artery disease, where atherosclerosis can occur without producing symptoms or signs. Some members of our control group may have latent atherosclerosis. Secondly, if we assume that our dietary is abnormal and that diet can influence serum fatty-acid patterns, then the serum fatty-acid patterns from both our groups are abnormal. Thirdly, abnormal diets will not necessarily produce the same metabolic changes or alterations in blood coagulability in every person. We could find no evidence of unnatural fatty acids in the serum of apparently normal people or in that of patients suffering from coronary-artery disease. Gas/liquid chromatography using polyethylene glycol adipate as the liquid phase has the disadvantage, however, that acids with one double bond cannot be separated from their isomers. Sinclair (1959) has suggested that this might also apply to acids with two double bonds and that what had been identified by gas/liquid chromatography as *cis*18:$2^{9\ 12}$ (linoleic acid) might be an isomer of it, with different biological properties. Böttcher et al. (1960a) have shown that the 18:2 acid in aortic plaques is largely *cis*18:$2^{9\ 12}$ (linoleic acid). Probably this finding also applies to serum.

To decide whether our dietary leads to a deficiency of unsaturated fatty acids or to the presence of unnatural fatty acids in the serum, study of the serum fatty-acid patterns in other populations who are known to have a low incidence of atherosclerosis might be helpful.

Böttcher et al. (1960a) have published data on the fatty-acid patterns of the lipids from aortic atherosclerotic tissue. It is tempting to compare the serum fatty-acid patterns of the atherosclerotic patients with those of aortic atherosclerosis in the hope that some light might be thrown on the method of atherogenesis, at least in the aorta. This approach, however, has certain limitations. Lipid in an atherosclerotic plaque might arise from seepage from the plasma, fatty degeneration in a mural thrombus, intimal hæmorrhage, or local synthesis by the vessel wall. These factors might act singly or in combination. It would be very difficult to decide what proportion of lipid in plaques was derived from each of the aforementioned factors. Furthermore: (1) it is doubtful whether a valid comparison can be made between serum fatty-acid patterns from Scottish subjects and atherosclerotic aortic fatty-acid patterns from Dutch subjects; and (2) the comparison of mean values and standard deviations between these two groups gives no clear indication of what occurs in individual patients. The comparison nevertheless yields interesting information (table II).

The fatty-acid composition of the cholesterol esters and the triglycerides of serum closely resembles that of aortic atherosclerotic tissue (stage II), except that there tends to be more oleic acid in the aorta.

The figures of Böttcher et al. for phospholipids have had to be amended for comparison with ours; they found substantial amounts of fatty acids of chain length longer than C_{20}, whereas our serum fatty acids were only analysed from C_{12} through C_{20}. It will be seen that there are substantial differences between serum and aortic phospholipid, the serum containing less palmitic, stearic, and arachidonic acids, somewhat more oleic acid, and considerably more linoleic acid.

Because of the similarity between the cholesterol esters and triglycerides in serum and those in atherosclerotic tissue, Böttcher et al. (1960a) have suggested that these fractions in the vessel wall arise from seepage from the plasma, although the higher content of oleic acid in the aorta indicates that this cannot be the sole explanation. Because of the differences between serum and aortic phospholipid, seepage of plasma into the vessel again cannot be the complete explanation; it seems necessary to postulate local synthesis or selective deposition of subfractions of phospholipids as suggested by Böttcher et al. (1960a).

Böttcher et al. (1960b) have also published data on the fatty-acid patterns of the lipids of atherosclerotic coronary and cerebral vessels. We would hesitate to compare our data for plasma with their data for the vessels, since the latter figures are based on a small number of samples, some of which were pooled. They noted no substantial differences between the fatty-acid patterns of the lipids of aortic atherosclerosis and those of the cerebral or coronary vessels, except that a lower content of linoleic acid was found in the cholesterol esters of the smaller vessels, especially those of the cerebral arteries. As their figure for linoleic acid was also below that for the corresponding acid in the cholesterol esters of the blood-plasma (Schrade et al. 1959), they suggest that this may indicate a relative impermeability of the vessel wall to polyunsaturated acids.

Their mean value for linoleic acid in the cholesterol esters of atherosclerotic vessels (stage II/III) from the circle of Willis was 25·5% (based on five samples). Certainly it is below our mean value for linoleic acid in the plasma-cholesterol esters, but the wide scatter of our figures suggests that more observations are needed before a conclusive opinion can be given.

Before attempting to read too much into these comparisons, it would seem desirable to determine not only the serum fatty-acid pattern of atherosclerotic patients before death, and the fatty-acid composition of their coronary and cerebral arteries, but also the fatty-acid composition of the aortic atherosclerotic plaques post-mortem, so that a comparison between serum and plaque composition could be made in the same patient.

Summary

Using gas/liquid chromatography, an analysis was made of the fatty acids in the three major lipid components of the serum from eighteen patients with ischæmic heart-disease. These results were compared with those of a similar analysis previously performed on the serum of sixteen apparently healthy subjects.

For most of the acids, including all the major components, there was no significant difference between the two groups. Small differences were present in a few of the minor components.

The serum fatty acids were compared with the fatty acids in aortic atherosclerotic tissue, the data for the latter being the figures of Böttcher et al. (1960a) who used a technique similar to our own. Except for a higher proportion of oleic acid in the aortic tissue, the fatty-acid composition of the cholesterol esters and triglycerides was similar. Phospholipids, on the other hand, differed considerably in their composition.

Comparisons were also made with the data of Böttcher et al. (1960b) for the fatty-acid composition of atherosclerotic coronary and cerebral tissue.

The implications of these findings are discussed in relation to certain hypotheses of atherogenesis.

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KINKING OF THE INTERNAL CAROTID ARTERY

in Relation to Cerebrovascular Disease

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TORTUOSITY, and even kinking, of the great vessels arising from the arch of the aorta is a well-recognised phenomenon. Honig et al. (1953) found 12 examples of kinking of the innominate artery in a series of 104 angiocardiograms. Parkinson et al. (1939) described 40 patients who presented with a pulsatile swelling in the neck, proved due to a kink in the common carotid artery. Deterling (1952) reviewed 89 cases from the literature. Kelly (1924 and 1925) described 150 patients with pulsation or swelling of the lateral wall of the pharynx, apparently due to a kink in the internal carotid artery in the neck.

Kinking of the innominate and common carotid arteries has been attributed to hypertension and arteriosclerosis. The elongation of the aorta resulting from these conditions is believed to push up the origin of the arteries and so lead to their kinking. For kinking of the internal carotid artery two causes have been postulated (Kelly 1925). The vessel is formed from the third aortic arch and from the dorsal aorta; hence, in the embryo, it is normally kinked. As the heart recedes into the thorax, the internal carotid artery is stretched and the kink eliminated. Failure of this developmental process might therefore account for persistence of the kink. The other cause suggested is elongation and tortuosity of the artery because of arteriosclerotic changes.

Hitherto kinking of the great vessels has been thought to be of minor clinical importance. A kink may cause difficulty in differential diagnosis by producing an opacity on a radiograph of the chest, or by appearing as a pulsatile swelling in the neck or pharynx. It may also trap the unwary surgeon. But kinks in the internal carotid artery have not been held responsible for cerebral symptoms. Quattlebaum et al. (1959), however, described 3 cases in which the development of hemiplegia was associated with a kink in the internal carotid artery. 2 of the patients also had non-obstructing atheromatous plaques at the carotid bifurcation. The kinked segments and the plaques were excised, and at follow-up examination, one, two, and six months after operation, the patients had had no further cerebrovascular episodes. It is also noteworthy that 1 of the 2 patients with kinking of the internal carotid artery described by Hsu and Kistin (1956) had previously had a transient hemiparesis.

It is always difficult to be certain of the relevance of any factor to the production of cerebrovascular symptoms. Cessation of symptoms after removal of a factor does not establish the existence of a causal relation between the two. It is well recognised, for example, that transient ischæmic episodes may cease spontaneously; hence, the disappearance or non-recurrence of symptoms following the excision of a kink in the internal carotid artery must be interpreted with caution. Nevertheless, the present unsatisfactory state of therapy for cerebrovascular disease demands that each potential method of treatment be thoroughly assessed.

There are two possible ways of assessing the significance of a kink in the internal carotid artery in the production of cerebrovascular symptoms. One is to submit a series of patients to resection of the kink and to estimate the benefit gained. The other is to seek circumstantial evidence by inquiring into the presence of cerebrovascular disease in these patients. If this latter method were to provide evidence that kinks are not innocuous, recommendation of excision would then stand on firmer ground.

This study was undertaken: (1) to discover the incidence of kinks in the internal carotid artery in the neck as revealed by angiography; (2) to seek evidence as to its cause; and (3) to assess its significance in the production of cerebrovascular symptoms.

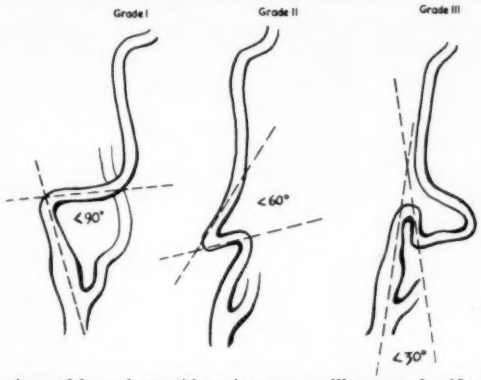
Method

A consecutive series of 1000 angiograms was examined by three observers.

All the angiograms had previously been reported as showing no significant abnormality, and the site of puncture in each was sufficiently proximal to enable the internal carotid artery in its entire length to be visualised. The reasons for angiography were those commonly found in neuroradiological practice—suspected cerebral tumour, aneurysm, arteriovenous malformation, subdural hæmatoma, intracerebral hæmorrhage, and cerebral thrombosis. Those in which a kink was present were classified into three groups according to its severity. The incidence of previous cerebrovascular incidents in the group with the most severe degree of kinking (group III) was ascertained, and compared with that in a control group obtained by a random process from among the angiograms without a kink in the original series of 1000. Some of the patients with the severest kinking were re-examined, special attention being paid to the effects of rotation of the neck.

Results

For the purpose of the study, kinking was considered to be present when the angle between the two segments of the vessel forming the kink was 90° or less on one film (see figure), or when the vessel formed a complete loop. There were 161 such cases, an incidence of 16%. The age and sex distribution of these cases are given in



Tracings of lateral carotid angiograms to illustrate classification of kinks according to severity.

table I. This shows that examples of kinking were present in every decade examined.

The 161 cases with kinks were subdivided into three groups according to the severity of the kink:

Group I comprised those cases in which the acute angle between the two segments forming the kink measured between 90° and 60°. There were 66 cases in this group.

Group II comprised those cases in which the angle of the kink was between 60° and 30°. There were 35 cases in this group.

Group III consisted of those cases in which the angle was less than 30°, or in which the artery formed a complete loop. This group contained 60 cases.

The mean age and mean blood-pressure as recorded in the notes of the patients in the three groups were calculated

TABLE I—AGE AND SEX DISTRIBUTION OF PATIENTS WITH KINKS

Age (yr.)	Males	Females	Total
0–10	4	..	4
11–20	5	1	6
21–30	9	3	12
31–40	8	6	14
41–50	23	18	41
51–60	24	25	49
61–70	22	11	33
71–80	..	2	2
Total ..	95	66	161

to see if more severe kinking was associated either with advancing years or with rising blood-pressure. Table II shows no such tendency. If anything the reverse obtains, though the difference between group I and III is not significant. There is, therefore, nothing to support the view that kinking of the internal carotid artery is due to advancing years or to rising blood-pressure.

Relation to Cerebrovascular Symptoms

The possible relevance of kinking of the internal carotid artery to cerebrovascular symptoms was first explored by examining the case-notes of the patients in group III—namely, those with the most severe degree of kinking or with a complete loop. 14 of the 60 patients in this group

TABLE II—AGE AND BLOOD-PRESSURE COMPARED WITH SEVERITY OF KINK OF INTERNAL CAROTID ARTERY

—	Group I	Group II	Group III
Number of patients	66	35	60
Mean age in years	54	44	46
Mean systolic blood-pressure in mm. Hg	159	147	142
Mean diastolic blood-pressure in mm. Hg	96	87	88

had had a significant cerebrovascular incident. Of these 8 had had one appreciable stroke, 2 a single transient episode, and 4 recurrent episodes.

To assess the significance of this incidence of cerebrovascular episodes, comparison was made with a control group which was selected by a random process from the angiograms without kinks. The reasons for angiography in those patients did not differ significantly from those in group III (table III). The number and type of cerebrovascular episodes which had taken place in this group is given in table IV. Comparison of the 14 patients from group III who had experienced a cerebrovascular episode with the 8 patients from the control group by the chi-square test shows that the difference is not significant ($P > 0.1$). Recurrent episodes, however, might, on theoretical grounds, be considered a more typical manifestation of a kinked internal carotid artery than might a single episode. The incidence in group III of 4 patients

TABLE III—REASONS FOR ANGIOGRAPHY IN GROUP III AND CONTROL GROUP

—	Group III	Control group
Cerebrovascular accident	10	9
Subarachnoid hæmorrhage	7	8
Migraine	5	3
Visual-field defects and ocular palsies ..	3	5
Cerebral tumour	7	6
Epilepsy	9	15
Headaches	5	4
Miscellaneous	14	10
Total	60	60

with recurrent episodes was compared with the absence of such patients from the control group by means of Fisher's exact probability test. This gave a P value of 0·059 which is just outside the conventional 5% level of significance.

Clinical Findings

The final step in the investigation was to call back for examination 24 of the 60 patients in group III. These were chosen because they lived near the hospital, and not because of any feature associated with their condition. Each patient had a complete medical and neurological examination. Auscultation of the neck was carried out by two observers separately, but in no case was a bruit detected.

In all 24 patients, rotation of the neck to each side for two minutes was carried out, with the patient standing,

TABLE IV—INCIDENCE OF CEREBROVASCULAR DISEASE IN GROUP III AND CONTROL GROUP

—	Group III	Control
No evidence of cerebrovascular disease ..	46	52
Recurrent episodes	4	0
Transient episode	2	3
Single severe episode	8	5
Total patients with episodes	14	8
Total patients	60	60

and in 4 instances rotation produced subjective symptoms. Only 1 of the 4 had previously had a cerebrovascular accident though 4 of the cerebrovascular patients were examined. The side of the symptoms appeared to have no definite relation to either the side of the kink or the direction of rotation of the neck. The patient with recurrent speech disturbance and a kink in the right internal carotid artery felt paræsthesiæ in the left hand either when the head was turned to the left or when the right internal carotid was compressed. Thus, rotation of the neck to the left might have increased the degree of kinking. As

compression of the left carotid in this patient caused faintness, one might reasonably assume that the blood-supply to the brain was mainly through the left carotid artery.

Discussion

This study contributes little positive information about the cause of kinks or loops in the internal carotid artery. There is clearly no relation between the severity of the kinking and either rising blood-pressure or increasing age. The lack of relation with age, and the existence of a number of cases in the first three decades of life, support the view that the kinking is due, in some cases at least, to a defect in embryological development. Whether degenerative changes in the vessel wall play any part remains uncertain. If this factor were important, it is surprising that the group with the most severe degree of kinking was not older than the rest, because degenerative changes increase with age. Moreover, in a previous study Bull et al. (1960) failed to show any relation between clinical evidence of cerebrovascular disease and tortuosity of vessels at six sites in the carotid tree, of which the internal carotid in the neck was one.

Whatever the cause of kinking of the internal carotid artery, the important practical question is its significance in the production of cerebrovascular symptoms; and here the evidence, though not conclusive, is more definite. There are more cerebrovascular incidents in the patients with kinks than in those without, but the difference is not statistically significant. But it could well be argued that a kinked internal carotid artery is more likely to produce recurrent episodes than a single episode, because of variability in the degree of kinking dependent on such factors as rotation of the neck and its position during sleep. Comparing the incidence of recurrent attacks in group III with that in the control group shows a difference which falls just short of the conventional level of significance. There is, of course, nothing absolute about the 5% level; and, in plain terms, the odds are 17 to 1 against the difference between the two groups being due to chance.

The clinical evidence provided by the re-examination of the patients strengthens the suspicion that kinking of the internal carotid artery may not be entirely irrelevant to the production of cerebrovascular symptoms. A relation between the direction of rotation and the side of the kink or of the symptoms was not always found and need not be expected. Thus, compression of a carotid artery may produce symptoms when, because of a lesion on the opposite side, the cerebral blood supply is largely dependent upon the normal artery. Moreover, kinking is not infrequently bilateral.

If, sometimes at least, the kinking is congenital, and if increasing tortuosity is not related to cerebrovascular symptoms, why do patients with kinks appear to be more liable to recurrent episodes in later life? We noticed that not infrequently the kink was associated with minor degrees of stenosis presumably due to atherosclerotic plaques. It is also noteworthy that 2 of the 3 patients described by Quattlebaum et al. (1959) had small "non-obstructing plaques" present. The relevant factor for the production of symptoms by a kink may therefore be the presence of an atherosclerotic plaque. Kinking might provide conditions of blood-flow which would facilitate the development of plaques and so lead to the higher incidence of recurrent cerebrovascular episodes in patients with a kink. This possibility deserves further study.

In conclusion, though we have been unable to provide indisputable evidence for any connection between kinking of the internal carotid artery and the production of cerebrovascular symptoms, the evidence is suggestive. It certainly justifies careful consideration of surgical excision in patients with recurrent cerebrovascular episodes who have a kink, and in whom no other adequate cause can be found in the cerebrovascular or cardiovascular systems, and especially in those cases in which rotation of the neck produces symptoms.

Summary

1000 angiograms, previously reported as showing no significant abnormalities, were re-examined. 16% of them showed kinking of the internal carotid artery. The kinking was present in every decade and there was a strong suggestion that recurrent cerebrovascular episodes were commoner in patients with kinks than in a normal control group.

We wish to thank the Nuffield Foundation for their generous support of our studies in cerebrovascular disease of which this forms a part, and also the physicians to the National Hospital who permitted us to study patients under their care.

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PHÆOCHROMOCYTOMA CAUSING URETERIC OBSTRUCTION IN A CHILD

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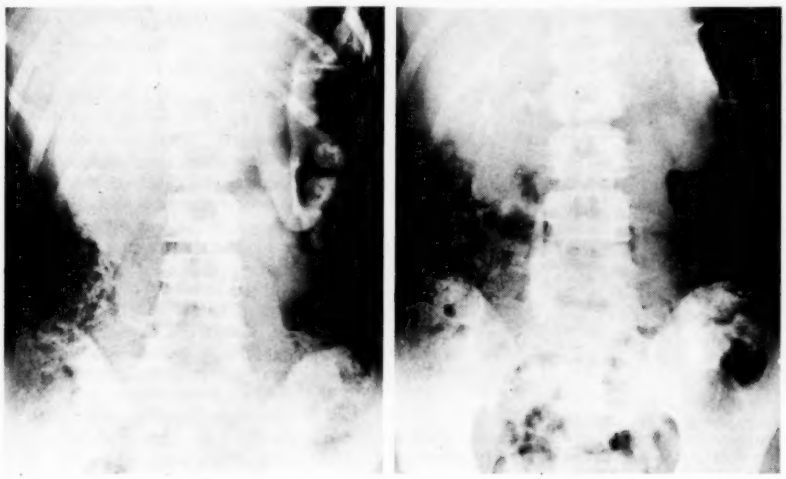
STRICTLY speaking, the term "phæochromocytoma" is limited to adrenal medullary tumours which turn a yellow-brown when treated with a solution of potassium dichromate. Tumours arising from extra-adrenal sites—e.g., the aortic bodies, the organ of Zuckerkandl, or the bladder wall—are referred to as paragangliomata. Since the name phæochromocytoma refers merely to the yellow colour, the view is now taken that any adrenaline-secreting or noradrenaline-secreting tumour, irrespective of its origin, should be called a phæochromocytoma (Symington and Goodall 1953).

Only 5% of reported cases of this tumour were in children (Nelson 1959) and, in them, 85% originated in the adrenals (Tevetoglu and Lee 1956). It follows that less than 1% of all phæochromocytomata are of extra-adrenal origin in a child.

Case-report

A girl, aged 12, was referred to hospital in February, 1960, with a history of three episodes of left-sided abdominal pain during the previous fortnight. These attacks had been followed by nausea and vomiting, but were unaccompanied by urinary symptoms.

She had complained of headaches intermittently since July, 1959. In January, 1960, she had become anorexic, and she had lost some weight. There was no history of paroxysmal flushing, sweating or palpitation.



(*a*) (*b*)

Fig. 1—(*a*) Film taken 15 sec. after injection of 40 ml. hypaque into antecubital vein showing faint opacification of entire renal substance on both sides; (*b*) film taken 5 min. later showing excretion of dye on right side only.

Clinical and Laboratory Investigations

The patient was a thin pale girl who appeared nervous and emotional. The facies and general demeanour vaguely suggested thyrotoxicosis, though exophthalmos and tremor were not present. The blood-pressure recorded initially was 185/125 mm. Hg. There was no cardiac enlargement, and the heart sounds were normal. Examination of the chest revealed no abnormality, and there were no abdominal masses or tenderness. Bilateral papillœdema with venous engorgement, unaccompanied by hæmorrhages or exudates, was seen on ophthalmascopy. The urine contained some protein, but there was no glycosuria. The erythrocyte-sedimentation rate (Westergren) was 59 mm. in the first hour. An electrocardiogram was compatible with early left ventricular strain. Radiological appearances of the chest were within normal limits. Cholecystography showed that an opacity in the right subcostal region was a gallstone.

Intravenous pyelography showed normal excretion by the right kidney, but no excretion by the left. The bladder appeared normal on cystoscopy, but the ureteric catheter could not be passed more than 2 cm. up the left ureter. A nephrogram was carried out by the method of Wall and Rose (1951), 40 ml. of ' Hypaque ' being given as rapidly as possible into an antecubital vein. This produced a faint outline of the entire renal substance on both sides (fig. 1).

A possible diagnosis at this stage was hypertension due to unilateral renal ischæmia, but it was difficult to find a cause for ischæmia. The girl's pallor suggested a peripheral vasoconstriction since her hæmoglobin level of 12·1 g. per 100 ml. was satisfactory. The catecholamine content of a 24-hour collection of urine was very high—800–1200 μg. per day (upper limit of normal 200 μg. per day).

The paroxysmal nature of the hypertension became apparent when the patient was kept under observation; and the blood-pressure once rose to 210/180. The variations in blood-pressure produced by an injection of 4 mg. phentolamine (' Rogitine ') intramuscularly are shown in fig. 2.

A tentative diagnosis of an extra-adrenal phæochromocytoma causing obstruction of the left ureter near the bladder was made before operation. The patient deteriorated steadily, with repeated paroxysms of hypertension and with multiple bilateral retinal hæmorrhages. Treatment with phenoxybenzamine (' Dibenyline ') 10 mg. orally twice daily was started and effectively controlled the hypertensive paroxysms. This therapy was stopped 48 hours before the operation, which was carried out by Mr. S. Davidson on April 22. An intramuscular injection of 4 mg. phentolamine was given an hour before operation to minimise the risk of extreme hypertension during manipulation of the tumour.

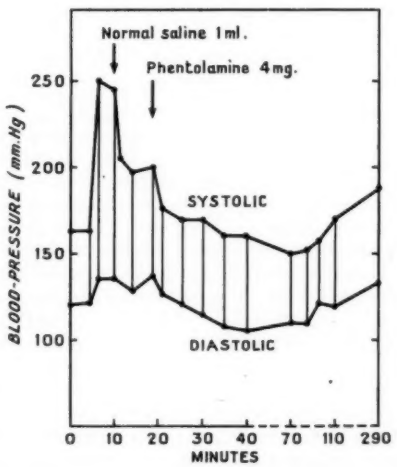


Fig. 2—Blood-pressure response to intramuscular injection of 4 mg. of phentolamine (see text).

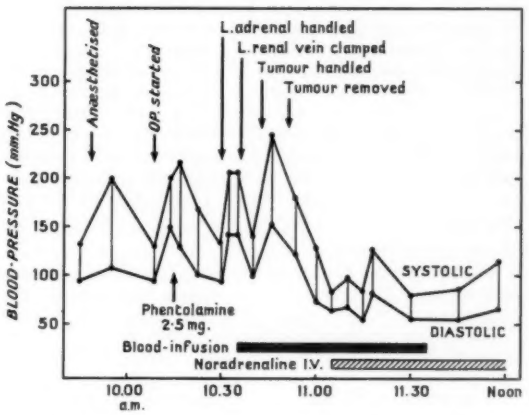
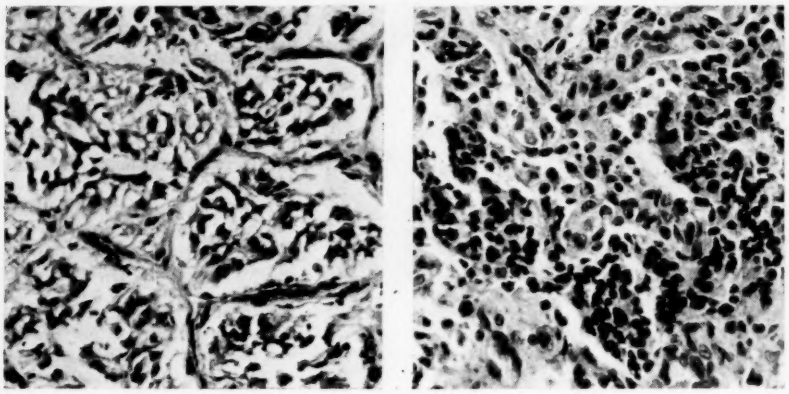


Fig. 3—Variations in blood-pressure during operation.

The Operation

A left oblique incision was made from the eleventh rib to the region of the anterior superior iliac spine. When the left adrenal gland was handled the blood-pressure promptly rose to 210/140 but fell to 160/100 immediately a clamp was placed on the left renal vein (fig. 3). A firm tumour was found encircling the left ureter, about 2 cm. above the bladder, and manipulation of the tumour caused a further rise in blood-pressure. The mass was mainly around the lower inch of the aorta and its



(a) (b)

Fig. 4—Photomicrographs of tumour: (*a*) well-differentiated tissue with mature phæochromocytes; (*b*) active pleomorphic area with some fibrous reaction and invasion of small blood-vessels. (×250.)

bifurcation, and the left common iliac artery; but it was impossible to determine the site of origin accurately.

The growth was adherent to surrounding tissues from which it was separated with considerable difficulty; but the bladder wall was not involved. The left kidney and adrenal were excised, the former because the degree of hydronephrosis was greater than expected. Complete macroscopic removal of the tumour was effected. The right adrenal was palpated and seemed normal. At this moment the blood-pressure dropped to 80/60 but responded satisfactorily to the slow intravenous infusion of *l*-noradrenaline which was used to maintain the blood-pressure at 100/70 for the next 24 hours.

The postoperative course was satisfactory. The improvement in her general wellbeing was dramatic, and the blood-pressure remained about 100/70. Proteinuria disappeared within a week of operation, and the urea-concentration test then gave normal results. Urinary catecholamine estimations 1 week and 1 month after the operation did not show pressor activity on biological assay. On biochemical estimation, the results were 50 μg. and 186 μg. per day respectively. The smaller retinal hæmorrhages were soon absorbed and disappeared. A single large hæmorrhage on the right side condensed, and papillœdema gradually improved. A month after operation the remnants of this hæmorrhage were the only discernible abnormality in the retinæ.

Pathological Findings

The left adrenal gland was normal and there was no evidence of a tumour. The tumour tissue was in three pieces. These were moderately firm, and the cut surfaces were yellowish. Histologically, the picture varied from that of a well-differentiated tumour showing mature phæochromocytes (fig. 4a) to that of a fairly active pleomorphic growth with some suggestion of vascular invasion (fig. 4b). All parts of the growth tested gave the chromaffin reaction.

The left kidney showed an early hydronephrosis with thickening of the pelvic epithelium indicative of infection of several months' standing.

Discussion

This patient presented in a most unusual way with abdominal pain as the main symptom. The finding of a gallstone might have led to dire results had an operation been performed without the protection of sympatholytic drugs. The paroxysmal nature of the hypertension was not apparent until the patient was kept under observation in hospital. Though the nephrogram was technically not all that could be desired, it did prove that the left kidney was present but not functioning. At this stage, a likely diagnosis was renal hypertension caused by an ischæmic kidney of the Goldblatt type. Doubt was cast on this idea by the character of the hypertension, the facial expression, and the pallor.

A phentolamine test was carried out (fig. 2), but the result was equivocal. On one hand, the paroxysm of hypertension, which occurred just before the control injection of normal saline, could be interpreted as leading to the drop in blood-pressure after the administration of phentolamine. On the other, the severity of a paroxysm of hypertension (250/140) produced by the sight of a hypodermic needle was clearly pathological. Estimation of urinary catecholamines gave such abnormally high results that the diagnosis was in little doubt, and the position of the obstruction 2 cm. above the orifice of the left ureter suggested a possible site for the tumour. The response to dibenyline gave further information. This long-acting drug controlled the hypertension but was discontinued 48 hours before operation in order to avoid persistent postoperative insensitivity to noradrenaline. To control the blood-pressure during the anæsthetic induction and early stages of the operation the shorter action of phentolamine was preferred.

Because primary growths are rare except in the adrenal gland (Symington and Goodall 1953), the left renal vein was clamped early in the operation to make handling of a possible intraglandular tumour less dangerous. This caused an immediate drop in blood-pressure (fig. 3), and for this reason the gland was removed. A tumour could not be palpated in the adrenal gland, which was, in fact, histologically normal. It is not clear why a drop in blood-pressure should have taken place when the left renal vein was clamped. Perhaps, even in the presence of a phæochromocytoma, the blood-pressure is maintained by the normal adrenals to a greater extent than one might think. The presence of an aberrant vein from the tumour to the renal vein seems unlikely.

The firm tumour mass encircling the left ureter low down and adherent to many structures gave the impression of local malignancy, but no distant metastatic deposits were seen or felt. The diagnosis of malignancy in these tumours has given rise in the past to a good deal of difficulty. As in this patient, many have appeared to be infiltrative in situ. Histologically there may be areas of pleomorphism, with infiltration of thin-walled blood-vessels, in tumours removed from patients who have remained well for many years afterwards (MacGregor 1960). Distant metastasis appears the only reliable criterion of malignancy (*Lancet* 1960). Symington and Goodall (1953) found 31 of these tumours, stated to be malignant, in 271 reported cases. In 19 instances there was insufficient evidence of malignancy when judged by metastasis, and 5 could be explained on the basis of multicentric origin, leaving 7 cases (2·5%) of undoubted malignancy. Stowens quotes the incidence of malignancy as 8%, but his criteria appear to be less exacting (Stowens 1960).

The examination of these tumours should include staining for the chromaffin reaction and assay of catecholamines from the tissue. The chromaffin reaction has long been regarded as capricious (Willis 1953), but Kennedy et al. (1961) found it reliable when a chromate/dichromate mixture of pH 5.8 was used.

Paper chromatography of a minced fragment of the tumour showed the presence of DOPA (3, 4-dihydroxyphenylalanine), noradrenaline, and adrenaline in the approximate proportions of 6/2/1. No dopamine (3-hydroxytyramine) was identified. McMillan (1956) suggested that these precursors (DOPA and dopamine) of

catecholamines are produced selectively by malignant tumours, but evidence against this has recently been shown (Kennedy et al. 1961).

The site of origin of this tumour remains in doubt; it probably was the organ of Zuckerkandl, but the tumour could have originated from any of the paraganglia related to the autonomic nerves in that region. In contrast to the case described by Farley and Smith (1959), which is the only other one known to us that presented with a non-functioning kidney, the tumour did not arise from the bladder. Cook et al. (1960) describe 3 cases of phæochromocytomata of the organ of Zuckerkandl and review 3 others. They noted abdominal symptoms as being the rule in such cases, ascribing them to compression of surrounding structures.

Summary

A 12-year-old girl complained of left-sided abdominal pain, headaches, and vomiting. She was found to have hypertension, papilloedema, and a non-functioning left kidney. A diagnosis of extra-adrenal phæochromocytoma obstructing the left ureter was made. The tumour was removed successfully. Some points arising from the operation and from the establishment of the diagnosis are discussed.

We should like to thank Prof. S. G. Graham for access to this case, Dr. J. J. Lewis of the department of experimental pharmacology, University of Glasgow, and our colleagues of the Royal Hospital for Sick Children and the Royal Infirmary, Glasgow, for advice and for carrying out the radiological, biological, and biochemical procedures.

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DANGER OF AIR EMBOLISM IN HIGH-PRESSURE BLOOD-TRANSFUSIONS

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VARIOUS types of pump are now widely used to restore the blood-volume rapidly in severe oligæmic shock (Melrose and Shackman 1951). Pumps have their dangers, however, and among these, the danger of air embolism can be disastrous. A number of cases of air embolism following the use of high-pressure transfusions have been described. In one, air was thought to have entered through the top of the filter candle when the level of blood in the bottle was low and the lower part of the filter was partly occluded with coagulum (Doyle and Frodsham 1949). In another, involving the use of the Martin pump, air was thought to have entered through perforations in the rubber tubing just above the pump (Langmaid and Mushin 1955). In the case described here, another source of air was responsible.

Case-report

A fit young woman who had had a normal pregnancy and labour was found to require evacuation of the uterus seven days after delivery. A few hours after the operation, she began to lose blood heavily and became shocked. She had a blood-pressure of 70/0 mm. Hg, a rapid pulse (almost imperceptible at the wrist), and peripheral vasoconstriction. She had to be returned to the theatre for packing the uterus, and to make her fit for the operation a rapid transfusion was necessary, for which the Martin pump (Martin 1954) was used.

Before and during the operation she received 5 pints of fluid (2 of 6% dextran and 3 of blood). Of this fluid 3 pints was given by means of the pump. The transfusion was given by means of a cannula tied into the long saphenous vein at the ankle. A constant watch was kept on the fluid-level in the drip-chamber and on the amount of blood in the bottle, to guard against massive air embolism. The patient returned to the ward in good condition, and her blood-pressure was 145/80 mm. Hg, although continued bleeding had eventually necessitated a hysterectomy.

A further pint of blood was running in slowly when she returned to the ward. She died suddenly about half an hour after the operation, when this bottle was still half full.

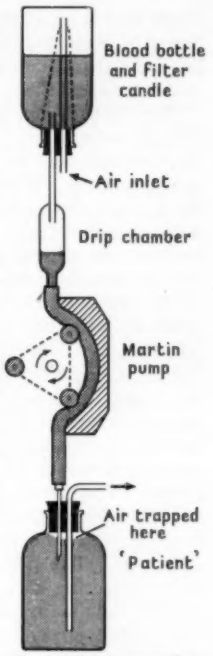

Fig. 1—Experimental apparatus for determining source of air bubbles during blood-transfusion.

A coroner's postmortem examination showed that death was due to air embolism. Although only a few millilitres of air had entered the patient's circulation, these proved fatal as they had entered the basilar artery, bypassing the pulmonary circulation through a widely patent foramen ovale. Although all the usual precautions had been taken with the transfusion (*Ministry of Health* 1958) the transfusion was thought the source of the air that had entered the circulation.

Experimental Investigation

A standard red-rubber-and-glass blood giving-set was assembled and the tubing and drip-chamber filled with water in the usual way. To represent the patient, a bottle was fitted with a trap for air bubbles and was completely filled with water. The needle of the giving-set was pushed into the rubber bung of the "patient" (fig. 1).

At first the drip was allowed to run freely under the influence of gravity. Small bubbles at once became trapped below the fluid-level in the drip-chamber, held

Fig. 2.

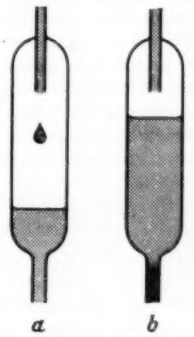

Fig. 3.

Fig. 4.

Fig. 2—Air bubbles trapped in drip-chamber.
Fig. 3—Drip-chamber before and after use of Martin pump.
Fig. 4—Drip-chamber completely filled with blood.

down by the rapid flow of the jet of water (fig. 2). Some of these bubbles would suddenly disappear from the drip-chamber, to appear a moment later in the " patient ".

The Martin pump was then attached to the rubber tubing just below the drip-chamber to simulate the way in which blood is given rapidly under pressure. When the pump was operated, the fluid inside the drip-chamber became churned up with bubbles of air, and a steady stream of small bubbles was seen to enter the " patient ". After a pint of water had been given in this way, the level of the water in the drip-chamber had risen—i.e., some air had been lost from the drip chamber—and this rise in level corresponded with a loss of 7 c.cm. of air from the chamber. The " patient " was found to contain 7 c.cm. of air (fig. 3). Repeating the experiment with the Higginson syringe, instead of with the Martin pump, attached to the air-inlet of the blood bottle gave essentially similar results. The newer Capon Heaton plastic disposable giving-set (Jenkins 1959) was liable to the same trouble, in this respect being no better than the old giving-set. The use of blood in the experiments made little difference, except that the bubbles were smaller and that it was impossible to see them below the fluid-level in the drip-chamber, thus giving a false sense of security. The result was the same—the level of fluid in the drip-chamber was seen to rise after the use of the pump, and 7 c.cm. of air was found in the " patient ".

Fig. 5—Filling the filter-chamber of Capon Heaton plastic giving-set.

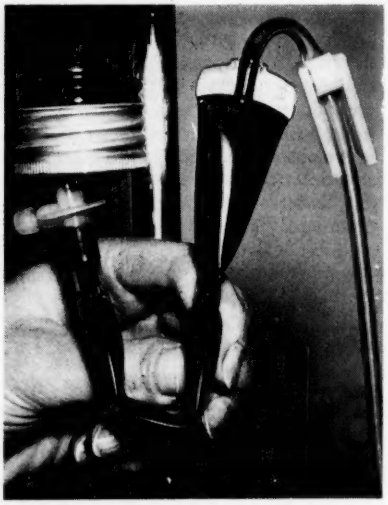

Fig. 6—First step in removing air bubbles from drip-chamber of Capon Heaton giving-set.

Discussion

The amounts of air are not great. Evidently with each pint of fluid given with the Martin pump about 7 c.cm. of air is given in the form of small bubbles. That this is not usually serious is shown by the large numbers of patients who have received transfusions with this pump without apparent ill-effect. This patient, however, had an unsuspected abnormality in the heart which allowed bubbles of air to bypass the lungs and to cause paradoxical embolism. Both auscultation of the heart and X-radiography of the chest were normal. A patent foramen ovale is not uncommon, and I have been informed of a similar case of paradoxical air embolism from a similar cause. Clinically unimportant patency of the foramen ovale has, in fact, been reported in nearly a quarter of all necropsies (White 1947).

All patients requiring rapid transfusions should be regarded as having a potentially patent foramen ovale.

Using standard apparatus, a safe method of transfusion which does not allow the giving of any air is possible if one simple principle is observed—namely, that if any form of pump is used to speed up the rate of transfusion, the drip-chamber must be completely emptied of air when the giving-set is assembled and filled with blood (fig. 4). This is easy with the standard red-rubber-and-glass giving-sets—the drip-chamber has only to be inverted during the filling of the set with blood, and all air will be displaced from below upwards as the chamber fills. To expel air from the filter-chamber and drip-chamber of the Capon Heaton disposable plastic giving-set is technically more difficult, but is possible if the apparatus is filled thus:

1. Having connected the set with the blood bottle in the usual way (Jenkins 1959), close the regulating clamp immediately below the drip-chamber and suspend the bottle and the air-filter tube from the drip-stand.

2. Gently squeeze and release the filter-chamber, avoiding frothing, until this is as completely full of blood as possible (fig. 5).

3. Bend the filter-chamber carefully (fig. 6) so that the drip-chamber, partially filled with blood, is inverted with the air bubble uppermost.

4. Remove the sheath on the air-filter tube that acts as an air inlet to the blood bottle, and gently release the regulating clamp. The drip-chamber will now fill with blood, expelling all air. The tubing of the set will fill with blood, and the drip-chamber may now be allowed to hang normally. If at this stage more air has appeared in the filter-chamber, this may be expelled by gentle squeezing. When all air has been expelled from the tubing, the drip-set is ready for use with the pump.

By the use of this technique, both the Martin pump and the Higginson syringe can safely be used without any danger. Using the same apparatus (fig. 1), no bubbles of air appeared in the " patient " even when blood was transfused at very high speeds. (The drip-chamber is not rendered functionless by filling it with fluid completely. It now works very well as an air-bubble trap should any air be delivered from the blood bottle.) The technique is easily mastered and is not time-consuming.

Summary

A maternal death took place from air embolism associated with the use of the Martin pump for blood-transfusion. The patient had a patent foramen ovale, and in this condition even small amounts of air may prove fatal. Experiments show that, when the Martin pump or the Higginson syringe are used, air from the drip-chamber inevitably finds its way into the patient. A simple technique for obviating this is described which should be employed whenever the Martin pump or the Higginson syringe is used for rapid transfusion.

I thank Mr. Philip Rhodes for his help and for permission to publish details of the case, and Dr. Donald Teare who performed the postmortem examination.

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Medical Societies

HEBERDEN SOCIETY

WHEN the society met in London on Feb. 10, the proceedings included a discussion of various aspects of ankylosing spondylitis.

Miss M. D. SNELLING discussing radiotherapy in the treatment of ankylosing spondylitis, suggested it should be used early in the disease when improvement in pain allowed the patient to receive vigorous physiotherapy, but once ankylosis was complete it was of no value. Of the various complications, skin necrosis no longer occurred with present doses, and though there was no absolutely safe radiation dose, leukæmia was unlikely.

Dr. J. W. STEWART described a study aimed at assessing the effect of radiotherapy on the bone-marrow during treatment of ankylosing spondylitis, and particularly at determining whether there was any pretreatment type of bone-marrow picture which was likely to progress to a leukæmic state. Of 105 patients in whom bone-marrows were obtained before therapy, only 44 were completely normal, the commonest abnormality being a generalised hypercellularity, although in a few this was limited to the erythrocyte or myeloid series and in 12 there was striking plasmocytosis. After the standard treatment of 2000r to the whole of the spine and sacroiliac joints, given as eight to ten treatments over three to four weeks, there was an immediate cessation of hæmopoiesis in the irradiated marrow. Recovery usually began three to six months after treatment stopped, but was incomplete, the bone-marrow remaining hypoplastic for many years. Of the patients who received two courses of irradiation at this dosage, in approximately half no recovery was observed, even after several years. In those who had 1200r there was again immediate cessation of hæmopoiesis after treatment, but recovery of the marrow began in three to six weeks, and was definitely more rapid and usually more complete than with the higher dose. Only 1 patient had developed leukæmia in the past four years and it so happened that this was the case in which no pretreatment marrow was available.

In the discussion, Dr. RICHARD DOLL, speaking for Dr. W.M. COURT BROWN, reported that 250r and 125r single skin doses to the spine resulted in chromosome abnormalities being observed in the peripheral blood for fourteen days. The value of deep X-rays in the management of ankylosing spondylitis was questioned by both Dr. H. F. WEST and Dr. R. M. MASON, who felt that it had no effect whatever on the course of the disease and just as good results could be obtained without it.

Mr. P. H. NEWMAN discussed the use of lumbar osteotomies of the spine for severe kyphosis secondary to ankylosing spondylitis. Elaborate preoperative and postoperative care was required. A disappointing after-effect was the tendency for the initial correction to slowly regress. This complication of ankylosing spondylitis was probably less common, now that more vigorous physiotherapy was used in the early stages of management.

Dr. F. M. ANDREWS reviewed the effects of prolonged treatment with oxyphenbutazone (G 27 202) ('Tanderil'). Of 38 patients maintained on this treatment, 31 had definite rheumatoid arthritis and 2 ankylosing spondylitis. The dosage was usually 400 mg. daily, but 2 received 500 mg. daily and 2 300 mg. daily. Salicylate was taken as required. The follow-up varied between fourteen and twenty-three months, and of the cases so far followed 16 required no other analgesics. The reduction in morning stiffness noted by these patients seemed important. 8 had stopped treatment for various reasons, 2 because of severe dyspepsia. This side-effect was seen in 4 others in a milder form and other side-effects were lymphœdema (not previously reported) in 2, ankle œdema in 4, mouth ulcers in 4, anorexia in 1, and pruritus in 1. No bone-marrow depression was seen.

Reviews of Books

Bedside Medicine

I. SNAPPER, M.D., director of medicine and medical education, Beth-El Hospital, Brooklyn, N.Y., and consultant in medicine, Veterans Administration Hospital, Brooklyn, N.Y. New York and London: Grune & Stratton. 1960. Pp. 592. 102*s*.

IN this delightful book is the distilled wisdom of a mature and brilliant physician, one whose experience has been worldwide, for in his time he has occupied chairs of medicine in Amsterdam, Peking, New York, and Chicago, and his many writings are widely known and appreciated. Now, in his eighth decade, he is still in active hospital practice and very far from being a "back number". In this book he discourses with equal fluency and authority on recondite subjects, such as phæochromocytoma, thalassæmia, and the nature of the autoimmune reaction in thrombotic thrombocytopenic purpura; on practical matters, such as the advantage that the stethoscope sometimes has over the X-ray tube; and on historical problems, such as the true nature of Banti's original "disease". There is no attempt to make this a comprehensive textbook. But Professor Snapper ranges over the whole territory of internal medicine, picking out some subjects for exhaustive analysis, others for discussion of some aspect only, and always he has something original and stimulating to say. He says it, moreover, in delightfully clear and terse English, with a refreshing absence of footnotes, cross-references, graphs, statistical tables, and other distractions; there is not even a bibliography. Anecdote is aptly used to point the moral when necessary.

The title is good. Not only is this clinical bedside medicine at its best, but this is a book to relax with after the day's work, to dip into at random with enjoyment; in other words, a book to keep at the bedside. The only drawback is that it is difficult to put down.

Chemotherapy in Emotional Disorders

The Psychotherapeutic Use of Somatic Treatments. FREDERIC F. FLACH, M.D., F.A.P.A., assistant professor of clinical psychiatry, Cornell University Medical College, New York; PETER F. REGAN, III, M.D., F.A.P.A., professor and head of the department of psychiatry, University of Florida College of Medicine. New York and London: McGraw-Hill. 1960. Pp. 314. 77*s*. 6*d*.

THE somewhat ambiguous subtitle indicates the content and purpose of this book. The authors rightly object to the exclusive use of either physical or psychological methods and advocate a "combined therapeutic approach" in psychiatry. But the advice they offer does not always escape the dangers of indiscriminate eclecticism.

The first part of the book deals with ætiology, classification, and interpretation of psychiatric disorders. A single page is devoted to physical factors, known and presumed, the rest being a fairly orthodox if uncritical exposition of freudian and allied views. No evidence is cited in support of some doubtful assertions (e.g., the invariably grave prognosis given for obsessional illness), and the authors' concept of schizophrenia seems much wider than the one current in this country.

The second part describes the indications for different physical and pharmacological methods in psychiatry, and the third part the treatment of various clinical entities—an arrangement which leads to repetition. Shock treatment is recommended "to overcome massive resistance in the psychotherapeutic treatment of a schizophrenic patient". On the use of newer drugs, little is said about their pharmacological actions, but much emphasis is laid on psychotherapeutic timing and implications; the reader may be left wondering whether they are regarded as placebos. While recognising that in depressive illness "the patients can undergo excruciating torture from their suicidal ideation and the emotional turmoil which accompanies psychotherapeutic exploration", the authors recommend intensive psychotherapy which "requires

that the patient remain in depressed states for months at a time"; they do not offer any evidence that this will either shorten the illness or improve the ultimate prognosis.

The Rickettsial Diseases

P. F. ZDRODOVSKII and H. M. GOLINEVICH. Translated from Russian by B. HAIGH, M.B. Oxford: Pergamon Press. 1960. Pp. 629. 105*s*.

THE second (1956) edition of this monograph has been brought up to date by the authors for this translation. The first part deals with the classification of the rickettsial diseases, the biology of rickettsia, and a detailed survey of experimental work on the subject. Of special interest is the account of the authors' own meticulous investigations which have not, we believe, been available up to now in any language other than Russian. The chapters on technical methods are as clear and cautious as they should be, and there is a warning on accidental infection which is plainly based on experience. The second part deals with each of the rickettsial diseases in turn: history, distribution, ætiology, experimental infection, clinical features, diagnosis, epidemiology, and prevention. Errors and omissions are negligible. It is a monument of learning and generous to workers in other lands. The authors have identified two benign rickettsial infections which do not seem to have been noticed outside the U.S.S.R.: there may well be more. The book ends with chapters on the pathology of rickettsial infections and on chemotherapy and specific prophylaxis.

This book is likely to remain the standard work of reference for many years and ought to be in every library. The illustrations (largely the authors' own work) are excellent, but the glazed paper used throughout makes the book heavy. The references to Russian and to foreign literature are well chosen and abundant. A final word of praise must go to Dr. Haigh who translated this book: the result is always readable and lucid.

The Reluctant Surgeon

The Life of John Hunter. JOHN KOBLER. London: Heinemann. 1960. Pp. 347. 21*s*.

THE *Encyclopædia Britannica* devotes more space to John Hunter than to Pasteur or Lister, Harvey or Jenner, Simpson or Freud. Such is the security of his place in history: yet his work is almost unknown to the general public, who are familiar enough with the names of the other men. This may be, Mr Kobler suggests, because his contribution to medical progress was a new mode of thought, a scientific discipline, and not an easily appreciated specific discovery or technical invention.

This study by a distinguished American journalist (he is an editor of the *Saturday Evening Post*) is intended for popular reading, but contains so much detail on Hunter's life that it will be of interest even to those well versed in the subject. How many who have seen Reynold's portrait know that John was also painted by the eccentric who sponsored Joanna Southcott's predictions about a new Messiah? It is common knowledge that Hunter treated Sir Joshua, and eventually performed a necropsy upon him: but the author reminds us that his patients also included Boswell's child, who had an undescended testicle, Gainsborough, who had malignant glands in his neck, and the infant Byron. Nor does this biography end with its subject's death, for an account is given of the exertions of the Army surgeon who, in 1859, with only one assistant, examined 3260 coffins so that Hunter's remains might be transferred to Westminster Abbey.

It must be admitted that the book throws no fresh light on the character of the central figure, and here and there falls into error. The Royal Society of Medicine was not so called until 1907, and the body from which it derived was constituted only just over a hundred years earlier, so Hunter (p. 294) can never have attended it. The embalmed bodies of Sheldon's mistress and Mrs. Van Butchell no longer "stand side by side" in the museum of the Royal College, for on a night in 1941 they suffered the same fate as thirty-seven thousand other more valuable, but less picturesque, specimens. No author, however, has yet collected in a single volume more information about Hunter's background, and no-one is likely to present that information more engagingly. This book should be the means of acquainting a much wider circle with "the dear man" who revolutionised surgery.

Dr. Ida

DOROTHY CLARKE WILSON. London: Hodder & Stoughton. 1960. Pp. 350. 21*s*.

BRITISH India of the last century teemed with pioneers who, if half the accounts are true, were larger in every way than life. Soldiers were braver than brave, rascals wickeder than wicked, and missionaries holier than holy. When these people fall finally into perspective, a prominent place must be accorded to two very remarkable women doctors who strove against the most appalling odds to help the purdah-ridden sick women of India. They were Edith Brown, from the English Plymouth Brethren, who created the Christian Medical College at Ludhiana in the Punjab, and Ida Scudder, the more warmly human of the two, the American who founded the Vellore Christian Medical College in South India. In personality, energy, appearance, skill, and dedication both women were outstanding, both were showered with honours, both died recently at a great age, and both remained active to the end. Edith Brown started her hospital first (in 1891) but Ida Scudder commanded the larger resources and built bigger. The continuing and expanding work of both colleges stands as a fitting memorial to each. They were women who made history, and history of the best possible kind.

Dr. Scudder's story is described here at length and with such local detail as to bring the early days and difficulties to vivid life, but the accounts of remote events tell more of the feelings of the author than of the subject. Some readers may think the tone too emotional and they might have preferred an equally sympathetic but briefer book, such as Francesca French's account [1] of Dame Edith.

Transactions of the International Society of Plastic Surgeons (*2nd Congress, London, 1959*. Edinburgh: E. & S. Livingstone. 1960. Pp. 589. 90*s*.).—In many countries today plastic surgeons are evolving new methods and techniques. The few textbooks are rapidly outdated, and English-speaking surgeons find it hard to keep track of new work in non-English-speaking countries. It was a rule of this congress, held in July, 1959, that all papers be in English, and these transactions, edited by Mr. A. B. Wallace, provide many important contributions from all over the world. The papers, each of which is followed by a summary in French, German, and Spanish, are arranged in 16 sections, covering every aspect of the specialty. The book is profusely illustrated and beautifully produced. It was not possible to allot time to all the papers submitted, and only the 91 selected for delivery are published. The remaining 122 are listed as "read by title"; some of them are perhaps unsuitable for summarising, but it seems a pity that a short résumé of many of the others could not be included. This is not just a book for the plastic surgeon; for there are no clear regional boundaries to plastic surgery. There are sections to interest orthopædic surgeons, pædiatric surgeons, dermatologists, dentists, E.N.T. surgeons, and ophthalmologists, eight papers on homograft research, and much of value to the general surgeon. Of course it is a heterogeneous collection; the style, presentation, and importance of the individual contributions vary enormously. On the whole, the editor and the scientific-programme committee are to be congratulated on their selection and arrangement. One of the best sections is on cleft lip and palate: it is the only one introduced by a general review of recent developments (by Dr. R. H. Ivy, one of the most experienced American plastic surgeons), which effectively sets the scene for the following papers. The value of the book as a work of reference would have been enhanced if most of the other sections had been similarly prefaced, and it might be a good plan at future congresses to invite papers on recent developments from senior men so that other contributions may be seen in perspective.

1. Miss Brown's Hospital. London, 1954.

THE LANCET

LONDON 25 FEBRUARY 1961

The Philadelphia Chromosome

EIGHTEEN months ago a somewhat speculative article in these columns on the perennially fascinating subject of the nature and cause of leukæmia [1] released a correspondence which was both entertaining and instructive, and which rapidly got down to fundamentals. SCHÖYER [1] invoked both a specific change in the white-cell precursors leading to lack of response to a circulating inhibitor, and a deficiency of the inhibitor. LAWS [2] challenged him to identify the specific change in the leucocyte. SMITHERS [3] denounced LAWS for clinging to the idea of a special "cancer cell" with a specific lesion. Subsequent argument hinged very much on the existence or absence of any "special evil" within the cancer cell. But the debate's most important contribution (as we can see it now) came near its end, when NOWELL and HUNGERFORD [4] reported finding a chromosome anomaly in two cases of chronic myeloid leukæmia. Since SCHÖYER had assumed that this form of leukæmia was due to deficiency of the circulating inhibitor, this finding seemed (if confirmed) to dispose of that part of his hypothesis, and incidentally of SMITHERS' argument. It has now been very fully confirmed. Short reports from the Edinburgh M.R.C. group [5] and from the original authors [6] are followed by the full report from Edinburgh on the first page of this issue. Here we have at least one kind of leukæmia, one kind of cancer perhaps, with a "special evil" in its cells.

The Ph[1] chromosome was seen in all 7 of the cases of myeloid leukæmia reported by NOWELL and HUNGERFORD [6] (who work in Philadelphia—hence Ph) and in 12 of 15 uncomplicated cases from Edinburgh. It is apparently not a new or extra chromosome, but simply one of the four smallest chromosomes (pairs 21 and 22, which are hard to tell apart) with about half its substance missing. Recognition of this abnormality demands preparations of a quality obtainable only with recent developments of the blood-cell culture technique (appropriately enough introduced by the Philadelphia group [7]), and earlier reports based on marrow cultures can be disregarded. The loss of substance by this small chromosome may be an actual deletion, or may involve transfer to another chromosome by translocation: gain (or loss) of so small an amount of chromatin would be hard to detect in a larger chromosome.

The variations in the proportions of cells containing the Ph[1] chromosome in blood-cell cultures from different cases, and its absence from skin cultures, indicate that only the actual leukæmic cells are involved: the normal cells of the patient, whether of blood or fixed tissues, have normal chromosomes. This is therefore not an inherent chromosome anomaly of all the cells of the patient, but something intimately bound up with the development of leukæmia: almost certainly a somatic mutation (in the broadest sense of the word mutation) in the patient's leucoblastic cells.

The Ph[1] chromosome has been reported only in chronic myeloid leukæmia, and apparently it must be present in at least the great majority of such cases. Three cases reported this week by Dr. COURT BROWN and his colleagues did not show it: this might be a technical failure, but the unusually slow progression in all three supports the view of these workers that they may represent a distinct brand of leukæmia. In chronic lymphatic leukæmia no such specific lesion has so far been shown. In the primary acute leukæmias there is again no specific chromosome pattern: some show nothing abnormal at all, some show irregularities of number varying in degree and type but roughly corresponding to those expected in malignant tumours, short of polyploidy.[8] (COURT BROWN, in a lecture in the Postgraduate Medical Federation's Scientific Basis of Medicine series in November, indicated that these variations might be somehow related to the ætiology of the acute leukæmias, but this looks like being a difficult subject.) When acute leukæmia arises as a complication of chronic myeloid leukæmia (as in three cases reported by the Edinburgh group) the Ph[1] chromosome may or may not persist. It is thus not always entirely safe to assume that in acute leukæmia the absence of the Ph[1] chromosome denotes that it has never been present.

The relationship with mongolism is tantalising. In mongolism there is an extra chromosome in pair 21, and also a high incidence of leukæmia. In chronic myeloid leukæmia there is a defect of a chromosome which must be either a no. 21 or a no. 22. Therefore, argue COURT BROWN et al., the Ph[1] chromosome must be derived from no. 21, the "mongol" chromosome, which must bear genes controlling leucopoiesis. Unfortunately the leukæmia of mongolism is acute leukæmia, and none of the mongol acute leukæmias examined by the Edinburgh workers showed the Ph[1] chromosome. It is not very easy to see just how deficiency of the genetic material of one chromsome can cause one kind of leukæmia, and excess of it another kind. Moreover, STEWART et. al.[9] thought that the high incidence of leukæmia in mongolism, so very well demonstrated by their series, might be explained by the high maternal age common to both mongolism and (a point not very well known) childhood leukæmia; and this hypothesis, which so far as we know has not been demolished, would remove the need to postulate any common basis in chromosome no. 21. We can only hope that these objections are illusory and the hypothesis will prove correct.

The discovery of the Ph[1] chromosome does not mean that we have found the "cause" of chronic myeloid

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3. Smithers, D. W. *ibid.* p. 569.
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9. Stewart, A., Webb, J., Hewitt, D. *Brit. med. J.* 1958, i, 1495.

leukæmia. It simply, after the way of such discoveries, splits the field of investigation into two more manageable halves—what causes the chromosomal defect? and how does the chromosomal defect cause abnormal behaviour by the affected cells? What is certain is that, if leukæmia can be regarded as a tumour (and most people nowadays would accept it as such), we have here, for the first time, an indubitable specifically labelled cancer cell.

Is it too much to hope that similar lesions of other chromosomes may underlie some other tumours? The gross chromosome abnormalities familiar in so many malignant tumours are a late and relatively non-specific feature. We know very little of the chromosomes of early tumours, benign tumours, or precancers. The techniques for their study are not yet comparable to those available for blood-cells. But it could well be that the Ph[1] chromosome is not a unique tumour-cell marker, but only the first to be discovered.

Tradition of Excellence

MAN'S progress is by accretion—by small or large additions to what has been done before. Our ancestors who made the rowing-boat or the wooden hut could not conceive the liner or the skyscraper; yet the new is only an adaptation and improvement of the old. The same is true of hospitals; and lessons for the future are most easily learnt from those that are at once ancient and very modern. The Massachusetts General Hospital, which has been celebrating its 150th anniversary this month, is an outstanding example; for, though "downright absent-minded about its past because it is immersed in the present",[1] it embodies a notable history alike of service, education, and innovation. Moreover, were he alive today, Oliver Wendell Holmes would be hardly exaggerating if he said again that it "has universally fostered a feeling of affection".

Amid the hospital's many later structures stands the original granite building with its central dome under which William Morton in 1846 gave the public demonstration which brought ether anæsthesia into general use. The surgeon who operated was John Collins Warren, who, with his medical colleague James Jackson, had been largely responsible for the hospital's existence. Another member of the staff in its early years was Henry Jacob Bigelow, whose discourse on self-limited disease, in 1835, helped to bring in a more rational use of drugs. In 1842 Oliver Wendell Holmes wrote his paper showing that puerperal fever was passed from mother to mother by the attending doctors. Then in 1869 another Collins Warren (grandson of the first) brought Lister's methods of antisepsis back from Glasgow and became one of the most tenacious of their American exponents. When asepsis followed, Maurice H. Richardson and other surgeons at the Massachusetts General were able to act on the advice of their pathologist, Reginald H. Fitz, who in 1886 recommended removal of the inflamed appendix to prevent peritonitis. Fitz's paper pointed the way towards effective treatment of abdominal emergencies, and three years after its appearance a special building for aseptic surgery of the abdomen and brain was opened at the hospital.

Interacting with the Harvard Medical School, the Massachusetts General was one of the first hospitals to plan clinical research; and what was a novel idea when Jackson started his bedside investigations has now become so pervasive that every spare corner seems to house an electron microscope or be used for collecting some kind of new data. The first real laboratory was opened about 65 years ago under James Homer Wright, the pathologist; but, though he "created an air of scientific excitement at the hospital", academic medicine and clinical research as nowadays understood did not really begin till 1912 when David L. Edsall was appointed chief of a medical service and Jackson professor of clinical medicine at Harvard, with a whole-time salary paid jointly by hospital and university. Edsall wanted research to be part of the life of the place—to encourage clinicians to bring their patients' problems to the laboratory and "the insights of science to the bedside". The group of young men whom he assembled and sent away for training elsewhere had as its nucleus Paul Dudley White, J. Howard Means, and George R. Minot; and in 1925 Dr. Means, as chief of medical services, was given charge of a research ward of ten beds "where cooperative patients with challenging problems could be observed and treated under the actual conditions of the laboratory". In this ward, so small yet now so famous,[2] Joseph C. Aub made his studies of lead poisoning, Means worked on disorders of the thyroid, Fuller Albright and his associates investigated hyperparathyroidism and other metabolic diseases of bone, and Walter Bauer laid the foundation of his research on arthritis and the pathology of connective tissue. A beginning was made in putting surgery as well as medicine on an academic basis when in 1922 Edward P. Richardson was made professor of surgery and chief of a surgical service: clinical investigation in medicine and surgery could now be a joint effort; and within a few years almost every service had a laboratory somewhere in the hospital. In 1938 a research council was formed to give all this work more coherence; but by the end of the second world war it was evident that

"continued progress demanded the development of a core of men and women who could throw all of their time and energies into the basic investigation of the underlying nature of disease. . . . Biochemists, biologists, physiologists, pharmacologists, nuclear physicists, organic chemists and radiation engineers were setting up shop at the MGH. A wedding of the biological and physical sciences was taking place, and a new science, biophysics, was developing with the addition of a new member to the Harvard-MGH partnership, the Massachusetts Institute of Technology across the Charles River in Cambridge".[1]

The position that basic science came to occupy at the hospital within quite a short time is indicated by the award of a Nobel prize in 1953, for the discovery of coenzyme A and its significance in intermediary metab-

1. Every Man Our Neighbor: a Brief History of the Massachusetts General Hospital, 1811–1961. By JOSEPH E. GARLAND. Boston: Little, Brown. 1961. Pp. 56.

2. Means, J. H. Ward 4. Harvard University Press, 1958

olism, to Fritz Lipmann, who had gone to the hospital as research chemist in 1941. Already in 1934 the general executive committee had said that the departmental walls between clinical investigators were coming down; and by the '50s there was evident need of similar demolition of the more resistant partitions separating the clinical researchers from the basic scientists, and the biological from the physical sciences.[1] In 1957 the philosophy of the research committee was expressed in these words by Paul C. Zamecnik:

" Three types of professional personnel were recognised to be essential to the future of the Hospital as a center for care of patients, teaching, and research: the practitioner busy on the patient front and yet interested in adding to the sum total of knowledge in his special field; the research straddler, engaged in translating the findings of the laboratory into terms of improved human welfare with minimum loss of time; and the Ph.D. and nonclinical M.D. personnel immersed in laboratories but sympathetic to their surroundings."

Nowadays, when the hospital's research expenditure is more than 4 million dollars a year—a fifth of its operating budget—the former director, Nathaniel W. Faxon, can fairly claim that the line of demarcation between clinical and basic research has disappeared.

But if to the outside world the Massachusetts General is known best as a citadel of science, it is still a general hospital for its community, of remarkably comprehensive scope. One unusual feature of the founders' objectives was their emphasis on mental disorder: what was wanted was described as " a hospital for the reception of lunatics and other sick persons ", and the institution for mental patients opened by the trustees in 1818—later known as the McLean Hospital—exemplified from the first the kind of " moral management " which favoured kindness rather than restraint, and, by concentrating on productive work, diversion, and exercise, offered treatment instead of purely custodial care. (Since 1935, when a full-time professorial unit in psychiatry was established in the general hospital under Stanley Cobb, some of the mental patients have been treated beside the " other sick persons ".) Secondly, the founders wanted their hospital to be for everybody, not simply for the indigent. Though the majority of patients could not pay the full cost of their care, and some could pay nothing, those who came to it were expected to pay the hospital what they could. A plan first mooted in 1863 was realised in 1917 when a block for private patients enabled the practising staff to earn at least part of their living in the institution where they did so much work without remuneration. A more unusual development came in 1930 when a large building was provided where people of moderate means have to meet only a single all-inclusive bill (with a ceiling for one admission) out of which the hospital pays the doctor. Meanwhile the Massachusetts General had forged closer relations with its community by meeting another kind of need. As long ago as 1905 Richard C. Cabot, as outpatient physician, used private funds to employ two full-time social workers in his department, and thus began what is regarded as the first medical social service in the world. Appalled by the problems of some of his patients, he concluded that hospitals have a social responsibility that does not start or stop at their doors.

That the Massachusetts General has remained a general hospital, responsible to the community and responsive to a wide range of needs, from emergency treatment to rehabilitation, is one reason for its continued success. But in moving into its fourth half-century it faces, as Dr. Means [3] points out, a world unlike any ever faced before, and he would have it broaden its front to encompass new necessities. Will it experiment with methods of bringing better integrated care to the patient, and in the improvement of human relations among all sorts of persons in its community? Dr. Dean A. Clark,[4] the general director, writes of the kind of comprehensive services the American people will almost certainly demand, and of the necessity of still seeing the patient as " the central focus of whatever we do ". " We must make sure ", he says, " that our fast growing research program doesn't overwhelm our functions of teaching and especially patient care." [5] With size and complexity come the risk of coldness and a loss of intimacy: it is hard, as Means says,[3] to be both scientist and humanitarian simultaneously. But it is, he adds, what modern medicine demands; and his hope that the demand will continue to be satisfied at the M.G.H. is supported by what Dr. George Packer Berry, dean of the Harvard Medical School, describes as the hospital's " tradition of excellence ".[5]

With Dr. Clark as general director and Dr. Walter Bauer and Dr. Edward D. Churchill as chiefs of the medical and surgical services, the Massachusetts General is governed by twelve trustees, some of them descended from the men who first conceived it. These trustees are appointed by a corporation of 63, one of whom, President Kennedy, opened the 150th anniversary convocation by a talk televised from Washington. On the afternoon of the same day, Dr. Benjamin Castleman, in the line of succession from Homer Wright, presided over a brilliant example of one of the hospital's most far-flung inventions—the clinicopathological conference devised long ago by Cabot and Wright and since made widely known through the *New England Journal of Medicine*. Otherwise the convocation, whose general theme was " to heighten the hope of man ", mainly consisted of symposia on scientific subjects, on nursing, and on the economics and future of medicine. The speakers included both many American authorities and many visitors from overseas, and at the concluding banquet the hospital paid a happy tribute to some of its seniors, coevals, and contemporaries. Ceremonially it presented commemorative medals to more than a dozen institutions as various as the Ospedale Maggiore of Milan (founded in 1456), the Hôtel-Dieu du Précieux Sang de Quebec (the first hospital of the New World), the Pennsylvania Hospital (first in the United States), and the All-India Institute of Medical Sciences (established in 1956 and represented at the convocation by the

3. Means, J. H. *New Engl. J. Med.* Jan. 26, 1961, p. 174.
4. Clark, D. A. *Boston Sunday Globe*, Jan. 22, 1961.
5. *Newsweek*, Feb. 6, 1961, p. 80.

Rajkumari Amrit Kaur). These in turn, and indeed all hospitals and centres of clinical research, may have something to learn from the partnership of Harvard University and the Massachusetts General Hospital—each at liberty to fulfil the functions for which it was designed but working together whenever their purposes coincide.

The M.G.H. was always intended to be, and always has been, a teaching hospital; and in this, Dr. Means thinks, lies its chief strength. Certainly as Mr. Garland says, the partnership has been productive in three respects: "It has given patients care of the highest quality; in the Hippocratic tradition it has helped to renew continuously the life-blood of medicine in Boston, in America and throughout the world; and it has created an atmosphere that excites keen minds to explore the dark continents of disease." From small beginnings, by accretion and selection, we see the hospital evolving into what is already, of its kind, among the greater of human achievements.

Annotations

STAPHYLOCOCCI AND DIARRHŒA IN HOSPITALS

PATIENTS in hospital who have had an operation and a course of "broad-spectrum" antibiotics sometimes develop diarrhœa which may be severe and even fatal. This is thought to be caused by antibiotic-resistant staphylococci and occasionally occurs in epidemics.[1] In a study of 243 inpatients with *Staphylococcus aureus* in the intestine, Dearing and Needham [2] restate some of the unsolved problems.

In the first place, is *Staph. aureus* always the cause? The relation of these organisms to their host is as varied in the gut as on the skin. They can be harmless commensals, as in the newborn: more than 50% of newborn babies are intestinal carriers by the time they are a week old, and 93% were found to be drinking staphylococci in their mothers' milk.[3 4] 17% of healthy adults carry staphylococci in their fæces, and in patients who have been in hospital for a week this figure may rise to 38%.[5] This high carrier-rate may lead to difficulty in diagnosis, for in some of these patients diarrhœa develops from other causes. Antibiotics alone may be responsible, either by direct action on the mucosa or by alteration of the bacterial flora; post-gastrectomy steatorrhœa may also cause diarrhœa.[6] Dearing and Needham found that 72 of their 243 patients recovered without treatment; but as the symptoms in most of them were mild, the staphylococci they carried may have been incidental. There is evidence that actual infection of the intestine with *Staph. aureus* is responsible for the more severe cases: in 6 such cases the diarrhœa stopped and the staphylococci disappeared when erythromycin, to which the organism was sensitive, was given [1]; in another series, rectal swabs yielded staphylococci in 10 out of 18 cases of severe diarrhoea but in only 27 out of 317 cases of mild diarrhœa.[7]

Although Dearing and Needham report that 27 of their patients had neither operation nor antibiotics, it is generally assumed that one or other of these predisposing factors is necessary for the disease to develop. Probably the most important element is the removal by the antibiotic of the normal intestinal organisms, so that resistant staphylococci flourish; and whether disease develops or not may depend as much on the resistance of the commensal organisms as of the staphylococci.

Staphylococcal enterotoxin differs from the other staphylococcal toxins, causing an acute but short-lived disorder when contaminated food is eaten. The enterotoxin is produced only by some strains; it is heat-resistant and gives rise to symptoms even when the organisms themselves have been killed. One might be tempted to suppose that staphylococcal diarrhœa of hospitals is due to local infection with enterotoxin-producing organisms and is a kind of continuous food-poisoning; but, as there is no simple and generally accepted test for enterotoxin, this remains a hypothesis. Surgalla and Dack,[8] by means of a feeding test in rhesus monkeys, found enterotoxin in 30 out of 32 strains obtained from cases of enteritis following antibiotic treatment. Other workers believe that there is no connection between staphylococcal food-poisoning and diarrhœa in hospitals: "Clinically the disease is an overwhelming local infection simulating cholera in its severe form, and there is no indication that enterotoxin enters the picture at all." [9]

Another problem is the connection between staphylococcal diarrhœa and pseudomembranous enterocolitis. This condition can only be diagnosed post mortem or, rarely, when necrotic membrane is passed in the stools. The disorder, which was known before the introduction of antibiotics and the appearance of antibiotic-resistant staphylococci, is thought to be a non-specific reaction to any severe intoxication, whether caused by diphtheria, uræmia, heavy-metal poisoning, or overwhelming bacterial infection.[10] Dearing and Needham carried out 21 post-mortem examinations; 6 patients had died from pseudomembranous enterocolitis, and the remainder from unrelated causes. In the second group they found no evidence of enteritis, although in some cases large numbers of staphylococci were cultured from the intestine. This confirms the opinion of other workers that staphylococcal enteritis is a reversible condition, while in pseudomembranous enterocolitis severe structural damage has taken place and recovery is unlikely.

Whatever the answer to these questions, staphylococcal diarrhœa is one of the evils of our hospitals; and if a virulent strain is involved and conditions favour cross-infection, some patients will suffer from being in hospital. An important factor in prevention is the differentiation of staphylococcal diarrhœa from diarrhœa with coincidental excretion of staphylococci. An excellent method for doing this has been described [1]: if examination of a direct gram-stained film of the fæces shows large numbers of gram-positive cocci in clumps, this strongly suggests actual infection with *Staph. aureus*.

Techniques for preventing staphylococcal cross-infection have been described many times.[11] Patients with diarrhœa who excrete large numbers of staphylococci are particularly important reservoirs of infection in a ward; and their isolation is essential. Broad-spectrum antibiotics should be replaced whenever possible by the

1. Cook, J., Elliott, C., Elliot-Smith, A., Frisby, B. R., Gardner, A. M. M. *Brit. med. J.* 1957, ii, 542.
2. Dearing, W. H., Needham, G. M. *J. Amer. med. Ass.* 1960, **174**, 1597.
3. Buttiaux, R., Pierret, J. *Ann. Inst. Pasteur.* 1949, **76**, 480.
4. Duncan, J. T., Walker, J. *J. Hyg., Camb.* 1942, **42**, 474.
5. Brodie, J., Kerr, M. R., Sommerville, T. *Lancet*, 1956, i, 19.
6. Dawson-Edwards, P., Morrissey, D. M. *Brit. J. Surg.* 1955, **42**, 643.
7. Brodie, J., Jamieson, W., Sommerville, T. *Lancet*, 1955, ii, 223.
8. Surgalla, M. J., Dack, G. M. *J. Amer. med. Ass.* 1955, **158**, 649.
9. Elek, S. D. Staphylococcus Pyogenes; p. 522. Edinburgh, 1959.
10. Hussar, A. E. *Lancet*, 1956, i, 506.
11. Williams, R. E. O., Blowers, R., Garrod, L. P., Shooter, R. A. Hospital Infection. London, 1960.

relatively insoluble sulphonamides, and careful watch kept for diarrhœa due to staphylococci—notably in patients who have undergone operation and have received antibiotics.

EXPERIMENT ON ANIMALS IN THE UNITED STATES

A BILL " to provide for the humane treatment of animals used in experiment " was introduced in the United States Senate last year by Senator Cooper and others and in the House of Representatives by the Hon. Martha Griffiths. It is based on British law and practice, with simplification of the procedure for granting licences and some modifications necessitated by the difference between the American and British constitutions. The problem of States rights has been circumvented by simply providing that no individual or institution experimenting on animals shall be licensed to receive a grant from Federal funds unless he or it has received from the Secretary of Health, Education, and Welfare a " certificate of compliance " with the requirements of the Act. These requirements relate, among other things, to the housing and husbandry of the animals, a pain rule, records, the suitability of an applicant for a licence, and the filing of a " project plan " setting out the methods and procedures to be used. The applicant's plan may be disallowed, but he must be given a reasonable opportunity to justify it.

An important difference from British practice is necessitated, no doubt, by the difficulty of introducing restrictions all at once into a vast research machine which is in full operation. In Britain permission must be given *before* an experimenter can use procedures of the kind or kinds which he specifies (with greater or less precision as the case may require) in his application for certificates. But when or if the Cooper Bill comes into operation as an Act, time will be needed to scrutinise all the project plans, which will have to be filed; and meanwhile research must go on, including perhaps some procedures which may have to be discontinued on later consideration. Presumably, while some procedures which are clearly unethical might be disallowed at once, most plans would have to be allowed provisionally pending review.

It would be unrealistic to hope that in every laboratory throughout the United States the treatment of animals can be brought overnight into conformity with the practice of the best American laboratories. Precedents will have to be created and standards agreed upon, and, although British experience may be found helpful, all this will take time. We may hope, however, that cruel procedures will be gradually eliminated, and also that the standard of husbandry in the least advanced American research establishments will be gradually raised towards that of the most advanced; and that the right to experiment will from an early stage be restricted to persons who are qualified to make proper use of it. These would surely not include schoolchildren, who at present are being encouraged in some quarters to repeat injurious experiments on animals.

The Bill is being somewhat fiercely assailed on one side by antivivisectionists and on the other by their more extreme opponents. The latter have represented British medical science as of inferior quality through a supposed frustration of medical research by Home Office control. For instance, an assertion which is widely current is to the effect that the British Act requires a separate document to be filed in respect of every individual animal used. In view of such allegations, the Universities Federation for Animal Welfare sent a questionary to all biological fellows of the Royal Society, and the replies have shown an overwhelming consensus in favour of Home Office control. As one of them says, " the Act of 1876 stops the frivolous but not the responsible worker ".

America's example in the treatment of laboratory animals will have widespread effects in other countries; the fate of the Cooper Bill will therefore be watched attentively.

RASHES AND VIRUS INFECTIONS

IN his Gordon Wilson lecture in 1956 Enders [1] considered new evidence about exanthems due to virus infections. He reviewed particularly his own work on measles,[2] that of Weller [3] on varicella and zoster, and that of Neva [4] on Boston exanthem. (The virus of Boston exanthem has now been classified as a member of the enterovirus family—ECHO 16.[5]) Since then many viruses, especially enteroviruses, have been found to be associated with rashes.

First, perhaps because laboratory workers were mainly interested in poliomyelitis, the association of virus excretion with meningitis and a rash, usually rubelliform but sometimes petechial or vesicular, was noted. This association was observed initially in the extensive outbreaks of ECHO 9 virus infection in 1956–58.[6–8] During these epidemics many cases displaying only fever and rash were seen [9]; and in children the rash was often confused with german measles. Detailed follow-up of women contracting ECHO 9 infections in pregnancy has not revealed any evidence of fœtal damage—although viræmia is known to occur sometimes in ECHO-9 infections.[10] The rash has been usually maculopapular but occasionally petechial,[11 12] in some cases being confused with that of meningococcal septicæmia. In fact, as Johnsson [13] pointed out, the association of meningitis with rubelliform rash had been noted earlier by Gabinus [14] in 1946 and Parry and Good [15] in 1948. Crawford et al.[16] described the isolation of a virus from similar cases during an outbreak in 1954; this virus has also proved to be ECHO 9 [15] Similar rashes have been observed in infections with Coxsackie viruses of groups B 1 and B 3, and ECHO types 2, 3, 6, 9, 14, 16, and 18.[17] Vesicular rashes have been associated particularly with Coxsackie A 16,[18 19] and Coxsackie B 3 [20] viruses. In these outbreaks, reported from Toronto,[18] Birmingham,[19] and Boston,[17] the rash was mainly on feet and hands, mouth, scalp, and neck. The lesions, which develop in crops, are associated with constitutional symptoms that are usually

1. Enders, J. F. *Amer. J. med. Sci.* 1956, **231**, 622.
2. Enders, J. F., Peebles, T. C. *Proc. Soc. exp. Biol., N.Y.* 1954, **86**, 277.
3. Weller, T. H. *ibid.* 1953, **83**, 340.
4. Neva, F. A., Zuffante, S. M. *J. Lab. clin. Med.* 1957, **50**, 712.
5. Neva, F. A., Malone, M. F., Lewis, L. J. *J. Immunol.* 1959, **83**, 653.
6. Boissard, G. P. B., Stokes, L. J., MacRae, A. D., MacCallum, F. O. *Lancet*, 1957, i, 500.
7. Berglund, A., Bottiger, M., Johnsson, T., Wermark, S. E. *Arch ges. Virusforsch.* 1958, **8**, 294.
8. Sabin, A. B., Krambiegel, E. R., Wigand, R. *Amer. J. Dis. Child.* 1958, **96**, 197.
9. Tyrrell, D. A. J., Lane, R. R., Snell, B. *Quart. J. Med.* 1958, **27**, 323.
10. Yoshioka, I., Horstmann, D. M. *New Engl. J. Med.* 1960, **262**, 224.
11. Laforest, R. A., McHaughton, G. A., Beale, A. J., Clarke, M., Davis, N., Sultanian, I., Rhodes, A. J. *Canad. med. Ass. J.* 1957, **77**, 1.
12. Frothingham, T. E. *New Engl. J. Med.* 1958, **259**, 484.
13. Johnsson, T. *Lancet*, 1957, i, 590.
14. Gabinus, O. *Svenska Läkartidn.* 1947, **44**, 835.
15. Parry, S. C., Good, R. A. *Publ. Hlth, Lond.* 1949, **62**, 163.
16. Crawford, M., Macrae, A. D., O'Reilly, J. N. *Arch. Dis. Childh.* 1956, **31**, 182.
17. Lerner, A. M., Klein, J. O., Levin, H. S., Finland, M. *New Engl. J. Med.* 1960, **263**, 1265.
18. Robinson, C. R., Doane Francis, W., Rhodes, A. J. *Canad. med. Ass. J.* 1958, **79**, 615.
19. Alsop, J., Flewett, T. H., Foster, J. R. *Brit. med. J.* 1960, ii, 1708.
20. Lerner, A. M., Klein, J. O., Finland, M. *New Engl. J. Med.* 1960, **263**, 1305.

mild—although in the Boston series there was 1 fatal case, in which virus was isolated from lungs and liver.

The differential diagnosis has included chickenpox, foot-and-mouth disease, and the Stevens-Johnson syndrome. In most of the outbreaks studied the responsible virus was isolated by tissue-culture methods. But the Coxsackie A 16 strains isolated in Birmingham would not grow readily in the tissue-culture system used by the investigators; and the virus was recovered by inoculation of suckling mice. This illustrates again the necessity of using a wide variety of methods in attempts to isolate virus.

A SURVEY OF EPILEPSY

THE bulk of fundamental research about epilepsy relates to the hospital-treated population, yet many people who have fits live normal lives without going near hospitals, so that little is known of the epidemiology of these disorders. Pond et al., in their survey of fourteen carefully selected general practices in England, covering a population of nearly 40,000 people, have therefore made an important contribution.[1] [2]

Their prevalence-rate of 6·2 per 1000 is a good deal higher than that in a similar survey in Minnesota (3·65 per 1000)[3] [4] and other less comparable estimates have also been lower. But elimination of two practices with by far the largest numbers of epileptics left an average over the remaining twelve of 5·6 per 1000. By age, the highest rates were found in the first year of life (almost 20 per 1000), dropping to 3·4 at 20–29 and rising again to 16·8 for the over-60s. The disagreement here with the Registrar General's figures [5] probably arises from different diagnostic criteria and age-groupings: the Minnesota study supports Pond's findings on age-rates. No difference was seen in sex-ratio (the usual finding has been an excess of males), and while social classes I and II were normally represented, a dearth of class-III epileptics was made up by a significant excess in classes IV and V. The young men in groups IV and V were more often single than in a normal population.

While about a quarter of patients had had attacks from infancy, in nearly twice as many fits began over the age of 20. Epilepsy itself carried little chance of shortening life, and only 1 or perhaps 2 of the 245 died in a fit during the year of study. Assurance companies should take note of this. It is disquieting to learn that in only about a quarter of the cases could the underlying cause of fits be diagnosed—and the difficulty was greatest in those between 15 and 60. This failure in diagnosis was not entirely due to lack of special hospital investigations, although what was done varied greatly according to the remoteness of the practice. Damage at birth and "febrile" fits predominated as clear causes; later injuries, tumours, and other lesions formed small groups.

Only 40% of the 245 had fits more often than monthly, and high frequency was correlated (not surprisingly) with both unskilled employment and the single state. Over half suffered major attacks (often with other types as well), a sixth had focal seizures, and very few indeed reported petit mal or myoclonic fits. A fifth, though clearly epileptic, could not be properly classified. Apart from petit mal (5 cases, all female) sex-distribution was equal. Even with the most refined techniques, classification is often tenuous, but 39 cases did appear to be of temporal lobe type. 20 of the 39 temporal lobe cases had "serious psychological disorders", but many had had a disturbed early life, and neither social class nor employment records seemed adverse. Some of the evil repute of temporal lobe damage may be due to case selection (it accounted for half the 32 mental-hospital admissions ever recorded for the total group). Evidently it does not damage the personality as much or as often as most psychiatrists have believed. Psychological difficulties in the whole group (29%) were mostly neuroses, but this diagnosis probably did not exceed that what would be "normally" expected.

That erroneous notions of epileptic disorders stem from policies of referral to hospital was further suggested by Pond and Bidwell's comparison of those referred (about half the 245) with those not referred. Uncertain diagnosis, ætiology, or treatment did not make referral more likely, but psychological disorder, disturbed environment, and frequent fits (in that order) most certainly did. 14 of 39 children at school during the study year presented "problems", usually of behaviour, and all but 2 of the 14 cases were associated with "home disturbance". (The Underwood report [6] of 1955 mentioned figures between 5% and 12% for all children needing to attend a child-guidance clinic.) In employment, similarly, about half had met difficulties but only 1 in 10 was unemployable—always by reason of multiple handicaps. Those with fits continuing from school-age onwards provided the hard core of serious problems. A fifth of all patients concealed their epilepsy, and no less than 19 (15%) of the adults admitted to driving cars, which, the authors conclude, means that there may be 6500 drivers with epilepsy on the roads of this country. All 19 had fits less frequently than monthly.

This valuable survey confirms again Tylor Fox's view that social stigma and disability are often greater than the medical disorder merits. A substantial majority of people with "fits" live normal useful lives, work steadily in good jobs, and are no more mentally disturbed than anyone else. Psychological trouble, when it does come, seems from these figures to arise most often from disturbances in the environment—engendered in part by the fits themselves. Even doctors have evidently taken too gloomy a view of epileptic conditions in some respects. At the same time the study shows the need for better medical facilities; and the sooner the Cohen Committee's recommendations [7] are introduced the better.

THE MAMMARY SOUFFLE

IN the later months of pregnancy, innocent murmurs can often be heard over the precordium. These murmurs result from increased cardiac output and blood-volume, often with anæmia. They are systolic and of ejection type, maximal in mid-systole; they are loudest over the base of the heart, especially in the pulmonary area, and become quieter on inspiration.

Another less common sound may be heard over the front of the chest during late pregnancy and lactation. This, the mammary souffle, was first described by van den Bergh [8] and has been further investigated in African

1. Pond, D. A., Bidwell, B. H., Stein, L. *Psychiat. Neurol. Neurochir.* 1960, **63**, 217.
2. Pond, D. A., Bidwell, B. H. *Epilepsia*, 1960, **1**, 285.
3. Kurland, L. T. *J. chron. Dis.* 1958, **8**, 378.
4. Kurland, L. T. *Epilepsia*, 1959, **1**, 143.
5. Logan, W. P. D., Cushion, A. A., General Register Office. Studies in Medical and Population Subjects, no. 14, 1958.
6. Report of the Committee on Maladjusted Children; para. 375. H.M. Stationery Office, 1955.
7. Central Health Services Council: Report of the Subcommittee on the Medical Care of Epileptics. H.M. Stationery Office, 1956.
8. van den Bergh, A. A. H. *Ned. Tijdschr. Geneesk.* 1908, **52**, 1104.

mothers at the Baragwanath Hospital, Johannesburg.[9] Of 165 Johannesburg mothers after childbirth, 15% had a mammary souffle lasting usually for several weeks. The souffle was also heard in the same proportion of mothers during the second and third trimesters of pregnancy, but not in the first three months. This murmur was maximal in the second or third intercostal space, more often on the left than on the right side. Arterial pulsation could usually be felt at the site of the souffle, and the murmur was obliterated by pressure lateral to the stethoscope. The timing of the souffle was late systolic with an early diastolic element.

The mammary souffle may mimic patent ductus arteriosus and aortic-valve disease but is distinguished by its disappearance with pressure.[10] The innocent systolic murmur of pregnancy does not disappear with pressure and is mid-systolic, though both it and the mammary souffle are louder with the patient lying flat.

The mammary souffle results from increased blood-flow to the breast via the anterior perforating branches of the internal mammary artery. A rather similar situation exists in coarctation of the aorta; in 80% of such cases enlarged collateral arteries are seen and felt on the chest wall, especially in the interscapular region.[11] Late systolic murmurs, which disappear with compression, may occasionally be heard over these collaterals; but more common is a late systolic and early diastolic murmur resulting from the aortic stricture itself. Such a bruit was heard, high in the interscapular region, in 85% of Wood's patients with coarctation.

FIRST-AID IN THE FACTORY

"IT is estimated that in Britain every day there are half a million skin injuries of sufficient size to need at least a first-aid dressing. Of these, one in every ten needs attention at a factory surgery or industrial health centre." Many of these trivial injuries still put a man off work for a day while he visits his doctor, or a casualty department for a dressing, because "only about 1% of all factories employing fewer than 250 people have any proper medical services, although they contain more than half the factory population"

The view of Lord Taylor and his colleagues at Harlow in their newly published *First Aid in the Factory*[12] is that the factory first-aider should carry out the *full treatment of minor injuries and ailments* as well as giving conventional first-aid to more serious injuries which are awaiting skilled medical care or transport. To treat minor wounds, he must know his job and his limitations; he must recognise the types of wound he may dress and those he should refer. There is no suggestion that he should become a semiskilled nurse; he does not work in isolation but as a member of a team, and for more than minor injuries he need only know what to do until the trained nurse, ambulance, or doctor arrives. But he must have adequate facilities for the job, and the Harlow group suggest a detailed supplement to the minimum contents of the first-aid box prescribed by law. They rightly retain the term "first-aider", but they have added to him the job of "trained lay dresser".

From their picture of the factory first-aider, they exclude detailed knowledge of transport of patients with major fractures ("this is a task for the skilled ambulance worker who is doing this every week"). On the other hand, they recognise the useful part he can play by knowing the special hazards of the factory, by encouraging the use of protective clothing, and by helping convalescent employees on the factory floor to complete their recovery at suitable work. In dealing with minor ailments he is in a similar position to "the sensible mother of a family in the home".

A manual for this type of first-aider needs above all to offer practical instruction over a limited area, and this the authors have successfully achieved. Theory has been kept to a minimum, and usually in small type. Obsolete first-aid practices such as "pressure-points", tourniquets, wound antiseptics, and hot-water bottles have been abandoned. Instead, emphasis is given to important principles, such as speed in getting a shocked patient to hospital for transfusion, and the need to withhold oral fluids in case immediate operation is indicated. There are up-to-date chapters on aspects particularly relevant to factory work, such as thermal and chemical burns (it is surprising to find electrical contact burns described as particularly painful); and they also include the care of the unconscious, gassing, artificial respiration, and eye injuries. A miscellany at the end includes recommendations for teaching and examining; and there is a small bibliography for the keen man.

This is an excellent and original attempt to provide a handbook for a particular type of first-aider—the man "in the factory and on the building site and farm, in the shop, office and warehouse".

DRUGS AND THE URETER

WHEREAS formerly renal and ureteric colic were treated by injection of morphine and atropine, some now favour the administration of propantheline ('Probanthine') bromide or similar relaxants, for which they claim at least equal success. Owing to the variation in severity and duration of the attacks, reliable clinical comparison is difficult. Similarly, scientific methods designed to register the contractions of the ureter have been criticised on account of the abnormal factors attending their application. In this respect the work of Murnaghan [1] in this country in studying the movements of the ureter by cineradiography and electromyography probably most nearly approaches the ideal.

Methods depending on the introduction of a catheter to register the intraureteric pressure have been suspected to be unreliable. Nevertheless Weinberg and Maletta [2] claim to have obtained consistent tracings by means of an electromanometer connected to a small ureteric catheter which had been introduced in the usual way. In each of 31 unanæsthetised patients the definite pattern of frequency and contraction pressure of ureteric peristalsis remained uninfluenced to any significant extent by the administration of drugs. Morphine and atropine given in normal dosage had no effect on the resting pressure or on the frequency, duration, or amplitude of the peristaltic waves. Similarly, little effect, apart from occasional and transient cessation of peristalsis, was observed after intravenous administration of 30 mg. of propantheline. The conclusion, at least from this experimental work, is that drugs commonly used against ureteric colic fail to influence ureteric pressure.

9. Tabatznik, B., Randall, T. W., Hersch, C. *Circulation*, 1960, **22**, 1069.
10. Scott, J. T., Murphy, E. A. *ibid.* 1958, **18**, 1038.
11. Wood, P. Diseases of the Heart and Circulation. London 1960.
12. First Aid in the Factory. By LORD TAYLOR, M.D., F.R.C.P. With the assistance of W. N. BOOTH, M.B., B. S. LAING, M.B., and A. ROSS, M.B. London: Longmans, Green. 1960. Pp. 130. 9*s.* 6*d.*

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2. Weinberg, S. R., Maletta, T. J. *J. Amer. med. Ass.* 1961, **175**, 15.

Special Articles

AMERICAN HEALTH SERVICES

The President's New Proposals

" The dramatic results of new medicines and new methods—opening the way to a fuller and more useful life—are too often beyond the reach of those who need them most ", said President Kennedy in a message to the United States Congress urging acceptance of a new health programme. Announced in Washington on Feb. 9, the six-point programme calls for a new health-insurance scheme for the elderly, besides Government aid to community health services, child health, reablement, and medical education.

THE OLD

Perhaps the most controversial proposals are those for insurance for old people. Pointing out that the annual income of people over 65 is half that of their younger neighbours, while their annual medical bill is twice as big, and that for one-tenth of aged couples hospital bills absorb over 700 dollars a year—more than a third of their income—the message proposes a health-insurance programme covering such bills under the existing Social Security scheme. The programme would pay for in-patient hospital services for a single spell of up to 90 days of hospital care (less 10 dollars a day for the first 9 days), for 180 days' " nursing-home " care immediately after discharge from hospital, and for community nursing and " home health services " for a limited time. The cost of hospital outpatient diagnostic services (in excess of 20 dollars) would also be covered. The benefits would be available to all persons (now numbering over fourteen million) aged over 65 and eligible for Social Security or railroad retirement benefits. The scheme would be financed by a small increase in the Social Security contributions. The message emphasises that every person could choose his own doctor and hospital, and that the scheme would not directly affect any service performed or fee charged by any doctor; and the practice of doctors and the provision of hospital services would not be supervised.

Complementary proposals, designed to encourage home and outpatient care rather than admission to hospital, call for Federal grants to States for the construction of nursing-homes and for improving nursing-home and home-nursing services. Legislation is proposed to enable the Public Health Service to create a bureau of community health. Emphasising that 6000 million dollars a year of the nation's resources is spent on hospitals, the message calls for research and planning in the best and most economical use of " these costly structures ", and calls for more grants for such research and for the construction of experimental and demonstration hospitals.

OTHER PROPOSALS

Turning to medical education, the President's message says that, in the next 10 years, capacity of medical schools will have to be increased by 50% (and of dental schools by 100%) merely to maintain the same ratio of doctors to population. But the ratio should be increased, because the United States has medical responsibilities in other lands, whereas it is at present importing rather than exporting physicians; moreover the number of applicants at medical schools has been falling. This fall is attributed in part to the high cost of medical education. Accordingly the message makes four proposals: (1) planning grants to be made to colleges to plan expansion and improvement of medical education; (2) matching grants to be made to help expand medical schools under a 10-year programme; (3) Federal scholarships to be given to talented medical and dental students in need of financial help (in amounts equal to 1500 dollars for a quarter of the newly entering students); and (4) a grant to be made to each school of 1000 dollars for each Federal scholarship, since the costs of schools far exceed the tuition fees. Similar formulations for nursing are being considered.

Since 1950, the United States has fallen from sixth to tenth place in the world's nations in saving infant lives, and a new National Institute of Child Health and Human Development is proposed; and appropriations for the programmes of the children's bureau would be increased. Finally, the message calls for an increase in matching grants for vocational reablement; and in matching grants for research construction and Federal payments for both direct and indirect costs of medical research projects.

DIFFERENCES OF OPINION

The health-insurance proposals are vigorously opposed by the American Medical Association and by many conservative members of Congress; in fact, a Bill with similar provisions, introduced by Mr. Kennedy when he was a senator, was defeated last year. A substitute law (the Kerr-Mills Bill) was enacted expanding Federal grants to States, to provide funds for old people unable to pay medical expenses. Eventually supported by the American Medical Association, this Bill would increase payment of Federal funds to the States for nearly two and a half million citizens over 65 on old-age assistance, and authorise additional sums to provide full or partial care for about ten million who might need help in paying their medical bills. But to get such assistance, the elderly have to qualify by a means test—in effect, they have to take a pauper's oath. Many of the States have not yet even taken one step to put the Kerr-Mills Bill into effect, either because they lack the funds to match the proposed Federal grants or because they have thought that it might be superseded; and if the new proposals are adopted it is uncertain whether that law will remain on the statute-books.

Financing of the insurance scheme through Social Security, the President says, will spread the cost of the health services in old age through the working years, " in a manner consistent with the dignity of the individual "; it will " meet the needs of those millions who have no wish to receive care at the taxpayers' expense, but are nevertheless staggered by the drain on their savings—or those of their children—caused by an extended hospital stay ". Opponents hold, on one hand, that the scheme will open the door to socialised medicine, and will unwarrantably increase the Social Security burden on workers and employers (especially since rises are already projected for 1963 and 1966); and, on the other hand, that three million persons not covered by Social Security will be left out in the cold. There has, so far, been less discussion of the project—in some ways more revolutionary in the American context—for Government concern over the most economical use of hospital resources.

" Over 6% of our national income ", said the President, " is being spent from public and private funds for health services. Yet there are major deficiencies in the quality and distribution of these services . . . The measures I have

recommended . . . constitute a necessary foundation on which to build."

Rough sailing is foreseen for the Kennedy plan at this session of Congress, but most observers do not think that the Social Security insurance scheme for the elderly can be blocked very long. They predict that, even if it is not adopted in full at this session, more and more of it will be passed in succeeding sessions.

ADMISSION OF PATIENTS TO HOSPITAL

THE Joint Consultants Committee has discussed with the Ministry of Health arrangements for the admission to public hospital beds of patients previously seen in private consultation.

The committee has advised the Ministry of Health that the preparation and management of waiting-lists for public hospital beds is wholly the responsibility of the consultants concerned and that, in so far as registrars, house-officers, or other subordinate medical officers assist in this, the overall responsibility remains with the consultant.

The committee agrees that, in view of this responsibility, care should be exercised by each consultant to ensure not only that urgent and semi-urgent cases receive their proper degree of priority, but also that non-urgent cases whether first seen at a private consultation, a domiciliary consultation, or in an outpatient department are admitted in an appropriate and fair sequence.

It has been said that from time to time non-urgent cases seen in private consultation are admitted to public beds sooner than they should be, having been given unjustifiable priority. Whether or not this has in fact happened the Joint Consultants Committee is not in a position to say, but the committee fully agrees that consultants should take steps to ensure that it never does occur and advises all consultants to this effect.

OPTION OF WHOLE-TIME OR PART-TIME APPOINTMENTS

THE Joint Consultants Committee has again discussed with the Ministry of Health the agreement reached a number of years ago that hospital boards should, at the time of making a whole-time consultant appointment, normally offer the option of whole-time or maximum part-time. The option was agreed on the understanding that consultants so appointed would be " prepared to devote substantially the whole of their time to hospital work and to give it priority on all occasions ". By hospital work is meant, of course, all duties that arise from a consultant's contract. It is important that the right to exercise this option continues and the joint committee reminds consultants of their obligation under it. A hospital board has a right to advertise for a whole-time post without the option, but the board should have adequate reasons for so doing. To state that it requires the whole of a consultant's time is not adequate. Under the agreement it can expect as much from him on a maximum part-time contract as on a whole-time contract.

This is a valuable privilege for consultant applicants and, to safeguard its continuance, the Joint Consultants Committee reminds consultants of its terms and their obligation under it.

The same obligations apply to a whole-time consultant who applies in due course to become maximum part-time.

Before Our Time

FRANCIS ADAMS

1796–1861

ON Feb. 26, on the centenary of his death, we salute the memory of Francis Adams, a great Scottish country doctor who was at the same time our finest medical classical scholar—*Doctissimus Britannorum*—and a keen observer of natural history. He lived and worked and studied in the village of Banchory and its lovely surrounding district in the valley of the River Dee about 18 miles from Aberdeen.

His translation of *The Genuine Works of Hippocrates* has been probably the most widely read of his works, but his masterpiece was certainly *The Seven Books of Paulus Ægineta* with its fine notes and commentaries that give us such a wide and clear picture of the medicine of antiquity. It was called " the finest venture in pure historical medical research in the English language " by the late Prof. Charles Singer, who was one of his great admirers and who described the interesting life and work and accomplishments of Adams in a delightful essay in his book on *New Worlds and Old.*

In 1844–45 Dr. Adams was president of the Aberdeen Medico-Chirurgical Society, and a hundred years later in 1945 I had occasion, as the society's secretary, to look for a portrait of him to put on the menu card of our society's annual dinner. In our university library I came across a reprint on an article on " Francis Adams of Banchory " by the late Prof. Lewis J. Moorman of Oklahoma, U.S.A., another of Adams' admirers, who had himself been a " buggy doctor " in the country before he became a hospital physician in Oklahoma City. The picture in the reprint turned out to be one of Dr. John Brown, as Dr. Moorman himself, and also the late Dr. David Rorie, pointed out to me in the weeks following our dinner.

THE BUST

In his article Dr. Moorman mentioned that a bust of Adams was presented to the University of Aberdeen by his second son, Prof. Andrew Leith Adams, F.R.S., of Cork, who incidentally was the discoverer of the dwarf fossil elephants of Malta. Mrs. Ella Hill Burton Rodger, I also remembered, had described " the strong features and sagacious expression " of the face on the bust in her book *Aberdeen Doctors.* So I set off on a quest for the bust.

It was nowhere to be found either in King's College or Marischal College, the two colleges of our university, and nobody had seen or heard of it. It had been placed in the senatus room at King's College, but this room had been given up as a senate meeting-place many years before.

No bust yet, but there was found in our university library a photograph of it and at least I knew then what to seek.

A few years passed with no further result. Then in 1951 the Scottish Society of the History of Medicine was to meet in Aberdeen for the first time, and so, thinking the bust would be a fine exhibit, I determined to have a last thorough search for it. But still I had no success. Then one day as I was leaving the university library with our librarian, his servitor, knowing of my quest, came up and told us that there were some old statues in the carpenters' junk store that had once been the basement floor of the brewery of Old Aberdeen. We hurriedly went there. The badly lit room was filled with tables and chairs and pulpits and other things, but near one end, on a table, we could dimly see two busts. But they turned out to be apparently those of Roman Emperors.

Still if the Romans were there, could Francis be far away? No! I found the missing bust under a table in the corner of the room. It was duly cleaned and restored, and shown to our Scottish Society for the History of Medicine.

It was a great thrill to have such a happy ending to my quest, for it is a far cry from Oklahoma City, U.S.A., to Banchory, Scotland. Still, as Thucydides has it:

ἀνδρῶν γὰρ ἐπιφανῶν πᾶσα γῆ τάφος

" The whole world is the sepulchre of famous men."

A BOOK

That was the end of the search but not of my story. Professor Singer saw a photograph of the bust in our society's *Proceedings* and wrote me as follows:

Dear Professor Craig,

I saw in the notice of the Scottish Society of the History of Medicine that you had discovered the long-lost bust of Francis Adams. I am very glad indeed to hear of this. I can well remember it as being in a sort of ante-room to the Library in which it occupied an honoured place. I went to visit it with Professor Harrower who was at that time Professor of Greek. He has been dead now, I think, for a great many years.

You may perhaps know that I possessed an excellent photograph of Francis Adams. It will give you a rather different impression to that of the bust. It is an extremely Scottish face, shrewd, humorous, and very intelligent—altogether a most satisfying and convincing likeness. I have given it to Dr. E. Ashworth Underwood, Director of the Wellcome Historical Medical Museum, 28, Portman Square, London, W.1. I am sure he will let you have a copy if you ask for it.

Relics of Francis Adams are extremely rare. I possess, however, his copy of Boethius *De consolatione philosophiæ* in a Plantin edition of Leyden 1590. At the back of this little book is a notice explaining that the bust which you have found was presented to Aberdeen University by his son, Francis.

Inside the little book is a letter from Francis Adams to his son, who was a Regimental Medical Officer in India. I enclose a copy of it. It is undated, but a little research would make finding the date possible. I thought of presenting both book and the contained letter—which is holograph—to Aberdeen University Library. I thought, however, I would like to consult you first, and, of course, I would like some assurance that these relics of one of Aberdeen's greatest sons would not be mislaid. I think it would be appropriate to have a little special case made for them.

Some years ago I wrote a short biography of Francis Adams which appeared in the Bulletin of the Johns Hopkins University. I have reprinted it in a volume of essays by myself entitled *New Worlds and Old* published by Messrs. Heinemann. I am daily expecting copies of that book.

Yours sincerely,
Charles Singer.

Boethius's book and the holograph letter, Professor Singer's happy gifts, are now safely lodged in an oaken case alongside the bust in our medical school library at Foresterhill. Bound in vellum the book carries an inscription in Latin in Dr. Adams' own writing, which says:

" A golden little book which I have read, re-read, and read yet again for nearly forty years and which I shall read often as long as I live. F.A., MDCCCLII."

JOHN CRAIG.

Conferences

BRITISH MEDICAL ASSOCIATION

The annual meeting of the British Medical Association was held in conjunction with the biennial conference of the New Zealand Branch in Auckland on Feb. 6–10.

Autoimmunisation Diseases

Dr. J. O. MERCER (Wellington) introduced the concept of autoimmunisation as a basic common denominator which might be responsible for rheumatic or collagen disorders, hæmolytic anæmias, and certain diseases of the kidney and of the thyroid gland. Certain tissues were capable of provoking plasma cells to produce antibodies which were hostile and destructive to the patient's own tissues. These immunologically competent cells elaborated antibodies which were carried in the serum-globulin fraction, and methods for their detection were being refined.

Dr. I. M. ROITT (London) described his work with Dr. Deborah Doniach concerning circulating autoantibodies against thyroglobulin or thyroid extract. These were demonstrable in high titres in chronic thyroiditis of both the goitrous (Hashimoto) and the atrophic (primary myxœdema) types, and in low titres in thyrotoxicosis and non-toxic colloid goitre, and in 10% of middle-aged women. In a study of 64 close relatives of patients with Hashimoto's disease, it was found that a third had thyroid disease and almost all had circulating thyroid autoantibodies. Of the remainder, with apparently normal thyroid glands, antibodies were found in 30%—a far higher proportion than that in the normal population. The fact that these antibodies are so commonly found in the absence of destructive thyroid disease suggests that they are not primarily responsible for the progressive destruction of the gland so characteristic of Hashimoto's disease. The vexed question remains, as Dr. MERCER put it, whether these antibodies are noxious or the harmless concomitants of the pathological condition.

Dr. R. J. WALSH (Sydney) considered that the introduction of the Coombs test was the first step towards understanding autoimmunity in hæmatology. There were now presumed or proven antibodies against red blood-cells, leucocytes, and platelets; those against the I antigen of the red cell led to acquired hæmolytic anæmias, and those against some platelet or capillary-wall factor might be responsible for idiopathic thrombocytopenic purpura. Dr. Walsh suggested that some provocative substance, such as chemical, viral, or bacterial, affected an antigen in such a way that this otherwise placid antigen suddenly led to the production of hostile antibody, and that this mechanism might be mediated by altered ribonucleic-acid metabolism.

Temporary Loss of Vision

The many causes of temporary loss of vision were enumerated by Dr. I. M. ALLEN (Wellington). They included local and general vascular disease, neurological disorders including multiple sclerosis, and such drugs as quinine, salicylates, lead, arsenic, and ganglion-blocking agents. Dr. G. L. GLASGOW (Auckland) had witnessed temporary loss of vision due to stenosis of the internal carotid artery; and he stressed the value of auscultation, which revealed a bruit in those with incomplete obstruction. Dr. D. ROBERTSON (Auckland) confirmed this view and added that early diagnosis and surgical intervention might prevent the development of permanent blindness and hemiplegia. Mr. FRANK LAW (London) suggested that vascular spasm was the commonest cause of temporary loss of vision. Mr. R. H. L. FERGUSON (Auckland) and others emphasised the need for anticoagulant therapy for early thrombosis, for

hæmodynamic crises, and with corticosteroids in the management of temporal arteritis.

Steroid Therapy

Prof. SHEILA SHERLOCK (London) indicated the value of corticosteroids when hepatitis pursued a fulminant, relapsing, or long-continued obstructive course, and when kidney disease complicated lupus erythematous or presented as the nephrotic syndrome. Dr. H. J. WALLACE (London) added severe pemphigus as another indication, and Dr. W. S. TEGNER (London) said that these drugs had eased the lot of the rheumatologist. Dr. W. D. WYLIE (London) declared that incipient adrenal failure must be anticipated for several years after treatment had been discontinued. He emphasised the necessity of additional intramuscular cortisone as an operative umbrella. Dr. W. E. HENLEY (Auckland) succinctly compared the decision to embark on steroid therapy with that of matrimony: it should only be undertaken " reverently, soberly, advisedly, and in the fear of God ".

Diabetes

Prof. RUSSELL FRASER (London) has had experience of medical hypophysectomy by pituitary implantation of yttrium in 100 patients with disseminated breast cancer and 10 with severe diabetic retinopathy. The treatment prolonged life of the patients with cancer by about fifteen months, and thus far it seemed to halt the progress of retinal changes in the diabetics. The most practical and objective way of assessing its value in diabetics was by serial retinal photography. In the year following yttrium implantation there had been no advance in retinitis, which otherwise tended to progress inexorably with fresh episodes of bleeding. After medical hypophysectomy patients needed substitution therapy with thyroxine permanently, and with cortisone temporarily; and their insulin requirements were halved. Postoperative hypoglycæmia had to be guarded against.

Hypoglycæmia was also a complicating factor of a rare syndrome described by Dr. D. W. BEAVEN (Christchurch). He had observed both diabetes mellitus and Addison's disease in 6 patients, and he reviewed these cases together with the 60 examples already reported. Before 1950 these patients died of adrenal insufficiency and infections; but since the introduction of steroids these complications were being superseded by hypoglycæmia. Professor SHERLOCK suggested that the coexistence of these two conditions would be of particular interest to those who supported the concept of autoimmunisation. It would certainly be worth assessing whether circulating autoantibodies or other suggestive abnormalities could be detected in this group.

Sarcoidosis

Dr. D. GERAINT JAMES (London) defined sarcoidosis as a broad-spectrum disease which presented to clinicians of every discipline. Because its investigation included routine slit-lamp examination of the eyes, chest radiography, and estimation of twenty-four-hour urinary calcium output, the management of the disease and its many facets remained the responsibility of the general physician. Corticosteroids were the only worthwhile treatment, for they alone favourably influenced the clinical, radiological, biochemical, and histological abnormalities. As a thoracic surgeon, Dr. C. S. DAFOE (Edmonton) favoured lung biopsy by limited thoracotomy, scalene lymph-node biopsy, and bronchial biopsy for obtaining histological confirmation, which was so necessary.

Staphylococcal Pneumonia

During 1959–60, Dr. G. KELLAWAY and Dr. HYLTON LE GRICE (Auckland) observed 48 patients with coagulase-positive staphylococcal pneumonia. In 15 the course was complicated by hypotension, oliguria, or anuria, due to shock and renal anoxia. Since this fulminant course often occurred in patients with chronic lung disease or following influenza, and since the causal staphylococcus was penicillin-resistant in four-fifths of instances, it was not surprising that the mortality-rate of staphylococcal pneumonia was 25%. Dr. D. R. HAY (Christchurch), who had carefully analysed staphylococcal septicæmia in the South Island of New Zealand, stressed the poorer prognosis of staphylococcal pneumonia associated with septicæmia. Dr. GERAINT JAMES felt that the figures revealed by both the Auckland and South Island surveys would remain important milestones. Data of future surveys would be compared with them to assess the impact of the new synthetic penicillin, methicillin, which was proving so effective in the management of penicillin-resistant staphylococcal infections.

Ulcerative Colitis

Mr. A. LAWRENCE ABEL (London) emphasised the need of early surgery for the fulminant case of ulcerative colitis. Corticosteroid therapy should be tried only for two or three days. He disapproved of ileostomy, preferring total colectomy with ileorectal anastomosis. In contrast, Mr. G. E. MOLONEY (Oxford) said that emergency surgery was rarely employed in Oxford, where the medical regimen of Witts and Truelove had proved highly effective. Dr. A. P. MILLAR (Sydney) and Dr. C. ALLAN BIRCH (London) both stressed the importance of supportive treatment, including a high-protein diet and potassium to replace continuous colonic loss.

Advances in Liver Disease

Professor SHERLOCK reviewed modern treatment of liver disease. Ascites could be controlled in the majority of cases by rigid dietary sodium restriction, and chlorothiazide or mercurials with potassium supplements; and spironolactone was added to this regimen if necessary. Intravenous mannitol as an osmotic (water) diuretic was considered for the remaining small group with resistant ascites. In reply to Dr. A. ROBERTSON (Brisbane), Professor SHERLOCK said that large doses, even up to 1200 mg. daily, of spironolactone were occasionally necessary. The undesirable sequelæ of diuretic therapy were low-sodium or low-potassium states, and hepatic coma. Other factors contributing towards or precipitating coma were infections, narcotics, and hæmorrhage, such as from bleeding œsophageal varices. Intravenous vasopressin had proved helpful in the emergency control of variceal bleeding. Liver-cell failure was usually too gross for such patients to tolerate surgical intervention, but if this were contemplated then portacaval shunt would probably be the operation of choice.

Prof. RUSSELL FRASER felt that corticosteroids might have undesirable effects in patients with liver disease, who were unable to detoxicate the steroid. If corticosteroids were necessary in the pregnant woman with hepatitis, then small doses should be administered. Dr. D. BEAVEN (Christchurch) had observed hæmolysis as a complication of hepatic cirrhosis and wondered whether corticosteroid therapy controlled it. Professor SHERLOCK replied that hæmolysis was often associated with diminished red-blood-cell survival in all types of liver disease. It might be due to an intrinsic defect in the red blood-cell, and steroid therapy was usually ineffective.

Pregnancy

Prof. T. N. MACGREGOR (Edinburgh) described pre-eclampsia as a common and treacherous condition associated with a high fœtal death-rate. Ideally, every patient whose blood-pressure during pregnancy rose to 140/90 mm. Hg should be treated in hospital. Rest, sedation, salt restriction, and diuretics were the basis of hospital management; but in some instances hypotensive therapy might be indicated. It was unwise to prolong treatment if there was no obvious improvement. Labour should be induced at a stage when there was a reasonable chance of fœtal survival. In fulminating pre-eclampsia, labour should be induced forthwith—in early pregnancy by rupture of membranes, but cæsarean section was probably preferable in late pregnancy.

Mr. A. DICKSON WRIGHT (London) stressed the difficulty of diagnosing appendicitis in the pregnant, and the high mortality-rate of both mother and fœtus. An adequate incision and gentle handling of the tissues were essential, preferably under spinal anæsthesia. He did not treat varicose veins in the pregnant, except by a light support.

Mr. J. S. BATCHELOR (London) said that, although backache was extremely common, it occurred in only 5% of the pregnant.

It was most commonly due to increased lumbar lordosis, and sometimes to spondylolisthesis or disc derangement. Surgical removal of prolapsed disc was rarely necessary. If it developed during early pregnancy a surgical corset might be useful, whereas in late pregnancy bed rest until delivery might be preferable. Patients who had previously been troubled by disc lesions often went through pregnancy without incident.

Hiatus Hernia

In a spirited discussion on the relative merits of the abdominal and thoracic route of approach for correction of hiatus hernia, Mr. DICKSON WRIGHT eloquently advocated the abdominal approach. Although perhaps technically more difficult, it provided a better repair. He always did a vagotomy to control reflux. Mr. G. FLAVELL (London) preferred to repair the hernia through the chest. The case for surgical repair of all hernias causing symptoms was strong. 30% of hiatal hernias gave rise to symptoms, and 10% resulted in stricture. The gravity of the condition in childhood was illustrated by Sir DOUGLAS ROBB (Auckland). In a series of 37 patients the trouble was found to be present at birth or soon afterwards, though a few cases presented in adolescence or early adult life. 10 of these patients required major operations in which the stricture was removed and replaced by intestine, as a plastic repair.

HALLUCINOGENIC DRUGS

FROM A CORRESPONDENT

INTEREST in the substances which induce psychotic symptoms has intensified for two main reasons: firstly, study of their action may shed light on the mechanism of psychosis, especially of schizophrenia; and secondly, there is the question of treatment, for it is concerning those disorders most resistant to ordinary methods (obsessional states, phobias, depersonalisation syndromes, and personality disorders) that claims have been made. The conference organised in London on Feb. 15–17 by the Royal Medico-Psychological Association was therefore timely, and such a meeting was, furthermore, a new departure for the Association. The term " psycholytic " was much used in preference to " hallucinogenic ", and is more appropriate in the therapeutic context, signifying the loosening of the ego boundaries.

Psychopharmacology

Hallucinogenic mushrooms have been known for hundreds of years and played an important role in Aztec culture. As Dr. A. CERLETTI (Basle) pointed out, mescaline was isolated in crystalline form as long ago as 1896, its chemical structure was known by 1918, and its clinical effects noted not long after. Within the past 3 or 4 weeks his laboratory had isolated two forms of lysergic acid amide from the Ololiŭqui plant—the first known naturally occurring forms of this celebrated and highly active drug. The hallucinogens so far known suggested the importance of substitution in position 4 of the indole nucleus and supported the view that the effects were related to tryptophane metabolism.

From his studies with indwelling electrodes, Dr. P. BRADLEY (Birmingham) found that while both lysergic acid diethylamide (L.S.D.) and amphetamine caused electrocortical alerting, the L.S.D. effect depended much more on environmental stimulation. Experiments using conditioning techniques seemed to show that while amphetamine acted directly on the midbrain centres, L.S.D. acted via those collaterals from the sensory pathways which provided the affective link with the reticular activating system—and this would account for the sensory distortions of L.S.D. Such work did not exclude effects elsewhere in the central nervous system (for example, Baldwin had shown links between L.S.D. and the temporal lobes).

From the psychological standpoint, Dr. P. MCKELLAR (Sheffield) regarded the effects of mescaline on thought processes as amplifying and " caricaturing " normal deviations. Thinking became loose and slipshod with loss of controls, and irrelevant associations intruded. This, and loss of ability to abstract (" concrete " thinking), called to mind schizophrenic thought, as did the occasional persecutory delusion, although the " half-belief " or misinterpretation was commoner. Such parallels between the thought of schizophrenics and " model " psychoses, however, lacked reliable objective evaluation in both cases.

Describing the mode of action of mescaline, Dr. J. R. SMYTHIES (London) admitted that almost nothing was known. Radioiodine studies had shown that most was stored in the liver and very little reached the brain, but whether some detoxication product caused the symptoms could not yet be said. It was surprising that so little had been done on the structure/activity relationship of parts of the mescaline molecule, in relation, for example, to cell permeability and site of action: more compounds needed to be synthesised and examined. Conflicting views as to whether mescaline inhibited or facilitated cerebral activity had been reconciled by his studies of rabbit occipital cortex, which showed phases of both inhibition *and* facilitation following light flashes, the inhibition coming first.

New Drugs

Psilocybin, one of the hallucinogenic principles of the Mexican mushroom, *Psilocybin mexicana*, had been studied in 137 subjects (normal and psychiatric) by Prof. PIERRE PICHOT (Paris) and his colleagues. Molecular structure and cross-tolerance showed similarities to L.S.D$_{25}$., but psilocybin was far less active and briefer (4 hours) in effect. Central automatic stimulation was noted, mainly sympathetic, and always caused mydriasis, but other changes varied. Mood change was followed by distortions, illusions, hallucinations, and alterations in body image—often of a gross nature. Addiction could be a risk. Though the emotions were of uncontrollable intensity, environmental stimuli much influenced the picture. Its future applications might be diagnostic, by unmasking or augmenting the outline of the underlying disorder, and therapeutic, by catharsis of unconscious material with full recall.

Sernyl was another drug of brief effect with similar therapeutic possibilities but, as Dr. BRIAN DAVIES (London) pointed out, it was a synthetic substance rather like pethidine, unrelated to the other hallucinogens, and it had been designed for intravenous anæsthesia. It was, in fact, the most potent analgesic known and gastrectomy had been carried out in clear consciousness with sernyl alone. Intravenous action was immediate, with numbness of the extremities, giving way to euphoria, depersonalisation, loss of empathy, and a two-dimensional impression of the surroundings. Orientation was clear and the subjects in touch, but he found it hard to describe his experiences. Symptoms were most acute within an hour, and the only neurological features were ataxia and nystagmus, though one of Dr. Davies's 12 normal volunteers had gone into a catatonic state for 20 minutes. Tests had suggested that the sernyl-state was closer to schizophrenia than that due to L.S.D., and might provide a link with sensory deprivation. Sernyl had proved useful in 6 of 8 difficult obsessionals, of whom 1 was on outpatient oral maintenance dosage.

Therapeutic Applications

Drawing on 8 years' experience at Powick Hospital, Worcester, Dr. R. A. SANDISON described the treatment process as a therapeutic relationship between physician and patient during which L.S.D. was given. Using it once or twice weekly for 4–8 hours, emotional tone deepened, thinking changed, regression (often painful) occurred, and unconscious material was abreactively released, often with intense illusions and hallucinations. Below the personal unconscious, archetypal material could be detected—this being the most important level of all. A therapeutic environment was required which permitted acting-out, yet was secure enough to prevent suicide and psychosis—the two dangers inherent in the method, though of some 500 cases treated he only knew of 1 in which subsequent long-standing psychosis could be related to the drug. But L.S.D. in the absence of a psychotherapeutic environment could be disastrous, and " working

out " of the material released might take up to 3 years, requiring the occasional intervention of the therapist.

A douche of cold water was poured over the therapeutic hopes by Dr. J. T. ROBINSON (Roffey Park), who was completing a controlled study of L.S.D., ordinary abreaction, and standard methods, in 87 patients treated in the same therapeutic environments. So far the standard methods seemed more effective than either abreactive technique at 10% level of significance, but his clinical material was not described.

Specific Problems

Cases with depersonalisation were usually thought to have a poor prognosis and, in general, Dr. M. H. DE GROOT (London) had confirmed this in a small series of cases, despite the use of psycholytic drugs. Subjective improvement did occur with cases of recent origin but where the symptom was but one feature of longstanding personality disorder, little benefit could be expected and hallucinogens must always be accompanied by other treatment.

A new approach to group therapy was offered by Dr. A. M. SPENCER (Worcester) in which 10 chronically neurotic women were encouraged to regress and act-out under L.S.D. in the presence of loving parental figures and in a child-guidance setting.

Criminal psychopathy is an even more obstinate (and dangerous) condition, and the work of Dr. G. W. ARENDSEN-HEIN (Holland) was of particular importance. A modern therapeutic regimen had helped many of his cases, but systemic L.S.D. treatment had been started for those who, being physically fit, non-psychotic, averagely intelligent, and anxious for recovery, were of longstanding severe psychopathic criminality and quite untouched by ordinary therapeutic contact. Under this regimen, abreaction took place, conflicts were revealed, resistance fell, and introspection and insight increased: a new capacity for human relationships was formed. The subjects showed less fear of L.S.D. than of other treatments and cooperated well. 14 of 21 cases were clinically improved though a longer follow-up was awaited. Dr. Arendsen-Hein was sure we should re-think our belief in the intractability of psychopaths: this method enabled us to penetrate deeply and bring about changes in personality formerly thought impossible.

L.S.D. had enabled similar contact to be gained by Dr. KENNETH CAMERON (London) with 10 severely obsessional adolescent boys resistant to milieu and psychotherapy, of whom 4 had materially benefited and one been made rather worse. L.S.D. was but one technique in a total situation—a point made more firmly by Dr. ISMOND ROSEN (London), who found that cases with mixed depressives and obsessional symptoms could respond to the drug, but the prognosis depended on the psychoanalytic treatment of the transference situation and of the material produced: there could never be a " psychoanalytic drug ".

Dr. MICHAEL FORDHAM (London) had even greater doubts about the long-term usefulness of L.S.D. which could lead to defensive splitting of the ego with increase in resistance: awareness of the unconscious was not necessarily therapeutic.

Dr. T. F. MAIN cast doubt on the validity of very early memories, which appeared as though a child of several months had that fully developed ego which all studies showed it had not. Dr. H. J. SHORVON (London) thought all regressive phenomena to be implanted by the therapist to support preconceived ideas on the origins of neurosis; and Dr. STEPHEN BLACK (London) recalled that spontaneous hallucinations occurred in perhaps 20% of hypnotic subjects.

Philosophical Aspects

It has long been wondered whether hallucinatory content derives entirely from the consciousness and experience of the subject, or whether some sources quite outside the individual might play a part: Mr. GORDON RATTRAY TAYLOR suggested that material should be catalogued from many places and many cultures, now that hallucinations could be induced at will. He was impressed by the similarity between drug hallucinosis and religious ecstasy and said that we should not ignore disturbing possibilities outside the framework of scientific theory: for example, he had been one of a number of people some years before who had " seen " a certain non-material cat under different circumstances, none of whom could possibly have influenced the others. Again, though much mystical experience could be accounted for by ego-splitting and depersonalisation, the sense of " inward meaning " was less easily explained. There seemed current possibilities that racial or other memories might be sorted in the glial cells of the C.N.S., and an interesting report from Russia told of hypnotically-induced memories being abolished by exposure to a very large magnet.

Mr. CHRISTOPHER MAYHEW, among others, shared personal experiences of psychosis and drug-taking—his own on behalf of B.B.C. television. 400 mg. of mescaline had given him the visual phenomena so well described by Aldous Huxley, but, more impressively, had altered his time-sense so that events lost their sequence and he drifted off into episodes of " timeless " ecstasy. He believed that the dreamlike state removed a filter, as it were, and enabled him to exist " outside " time—with the implication, of course, that the human personality could also exist outside time. Mr. RAYMOND MORTIMER, however, though he shared Mr. Mayhew's view of the value of the experience (each had found lasting æsthetic benefit from it, and become better able to grasp modern abstract painting) did not believe that any drug was likely to give us better understanding of the universe.

The Future

People who have had a certain experience may too readily assume that everyone else will benefit as much as they, and enthusiasts (as most of the latter speakers in the conference were) are not always the first to point out the dangers. Though a cult of " lysergic analysis " may be unlikely to spring up, it must be emphasised that these drugs are potent and carry risks of addiction, psychosis, and suicide—nor is it at all certain that only " prepsychotic " persons are at risk. Much more knowledge of good (and ill) effect is needed before L.S.D. can be introduced into the mental welfare curriculum. It remains a talking-point whether drug psychosis has most in common with schizophrenia, affective disorder, toxic delirious state, or extended temporal-lobe aura, and it is even more doubtful how far it is therapeutically effective. Though some papers were impressive and offered hope for the formerly hopeless, it is manifestly wrong to suggest that this treatment cannot be submitted to controlled scrutiny—and the sooner the better.

Public Health

Diphtheria in London and Birmingham

IN London, 3 children in all have died in the outbreak originating in Kensington; 16 are affected, of whom 7 are carriers.

In Birmingham, no further deaths have been reported since the 6-year-old boy died last week. 6 potential carriers are under observation.

The organisms isolated in both outbreaks have been *Corynebacterium diphtheriæ mitis*, and not the *gravis* type as we reported last week.

Respiratory Infections

Deaths from influenza in England and Wales numbered only 174 more in the week ended Feb. 11 than in the previous week—they totalled 1393—and the epidemic appears to be declining in most regions of the Midlands and the North. But the southern parts of the country have been more widely affected than previously. Further isolations of virus of variety A2 have been made.

Deaths from pneumonia totalled 2058 (2060 the previous week, and 657 in the corresponding week last year). Deaths from bronchitis (1719) were 170 less than in the previous week, but above the level in 1960 (705).

In the administrative county of London, 51 died of influenza, 140 of pneumonia, and 185 of bronchitis.

Parliament

A Financial Adjustment

ON Feb. 15, in introducing the National Health Service Contributions Bill, Sir EDWARD BOYLE, financial secretary to the Treasury, said that it was generally accepted that some part of the cost of the National Health Service should be met by the weekly payments of insured persons. Just how big that part should be was not a major political principle, but a financial adjustment. In his view the balance between taxation and contribution proposed by the Government was reasonable. The health service would still receive from the Exchequer £600 million, a sizeable fraction of the total estimated civil expenditure of £3530 million. He also stressed that what the House was debating was a financial adjustment and not an economic cut. The Government were not setting any arbitrary limit to the cost of the N.H.S. He agreed that it was the duty of the Government to satisfy themselves that the total burden placed on the contributor was not too heavy, and he believed that the contributions proposed in the Bill were not unreasonable. We must bear in mind the increase in average earnings since the N.H.S. started, the fact that for the past four years social expenditure, including expenditure on the health service, had risen more rapidly than the national income, and the fact that the Government had shown their intention to improve the standard of the service through their plans for hospital building.

Mr. DOUGLAS HOUGHTON pointed out that the proportion of the cost of the N.H.S. borne by the Exchequer had varied. In 1949–50 it was 76·3%; in 1956–57 it was just over 80%; by 1957–58 it had fallen to 75%. The present Bill would bring it down to 70·7%, the lowest Exchequer contribution since the service began. Had the Government put a ceiling on the budgetary cost of the service, and if so what was it? It was desirable for the whole country to have a firmer basis for financing the service than the caprice of the Government of the day. The new contributions would fall harshly on many people with below-average earnings. They would fall alike on people on short-time and with large families. The Bill was part of a stealthy piecemeal process of shifting the cost of the Welfare State from public to personal expenditure.

In the course of the debate Dr. DONALD JOHNSON reiterated his opinion that the Guillebaud report was "one of the most disastrous social documents of modern times". He was anxious to see the finances of our health services fundamentally reorganised, perhaps on the Australian model. Dr. BARNETT STROSS pointed out that in the past ten years the annual average increase of the cost of the N.H.S. was £12 million. To him that did not seem a frightening figure.

Mr. SELWYN LLOYD, who spoke towards the end of a protracted debate, rebutted the charge that the Government's proposals were an attack on the health service. He based his defence on the expected development of the service, its prospective cost in 1960–62 of £850 million, and the slowly increasing share of the gross national product which it had received over the past six years. The second reading was carried by 263 votes to 193.

New Year's Estimates

The Civil Vote on Account for 1961–62 [1] shows estimated net expenditure on the National Health Service in England and Wales at £534 million and in Scotland at £66 million—a decrease on last year of £27 million and £3 million respectively.

The Hardship Fringe

ON Feb. 16 Mr. KENNETH ROBINSON prayed against the regulation [2] increasing the prescription charge from 1*s.* to 2*s.* per item. He reminded the Minister of Health that his predecessor had invited the medical profession to cooperate for a trial period in the voluntary limitation of drugs prescribed. If the trial was successful, the Minister had undertaken to consider the abolition of the 1*s.* charge. Mr. Robinson was interested to know if the inquiry had in fact ever been started. The new charges had met almost universal hostility, perhaps most marked among doctors themselves. The Minister would ignore the doctors' views at his peril for they were the instruments of his policy. At the last increase costs rose because the doctors prescribed larger quantities to protect their patients from the worse effect of the charges. The Minister would no doubt remind the House of the measures to relieve hardship. But Mr. Robinson was still uneasy, especially about the people on the hardship line who were not in receipt of National Assistance. At present only 0·25% of all patients received refunds on grounds of hardship. Was that a true measure of what hardship there was? Clearly many people were just not going to the National Assistance Board. He also asked the Minister whether it would be possible to draw up a register of the chronic sick in each area, so that they could be automatically exempted from prescription charges. About £56 million worth of proprietary drugs were sold last year through the N.H.S. Was there no room for economy there? We needed a full independent public inquiry into the facts about the drug industry, drug costs and prices.

Mr. JOHN MACLAY, secretary of State for Scotland, said that the prescription charge had existed in one form or another since 1952 and he could find no evidence that it had made any difference to the working of the health service. The drug bill had increased from £35 million in 1949–50 to £92 million in 1960–61 and we must watch that it did not get out of proportion to what was possible, consistent with our other obligations. The Health Ministries had already introduced measures to secure economy. There had been comprehensive inquiries into prescribing practice. Doctors were being given as much information as possible through Ministry publications such as *Prescribers' Notes* and the new *Prescribers' Handbook*. In about six weeks the first issue would appear of a new journal, to be produced by outside experts, which would give the doctors objective valuations of new drugs. The new voluntary price regulation scheme for proprietaries concluded with manufacturers would cover about 85% of the cost of all drugs. Sample figures from a big practice [3] suggested that the number of prescriptions and the cost for the individual patient, even the chronic patient, were not as high as it might seem from some speeches. Eleven multiple packs were in use. Patients who had difficulty in meeting the charges could get refunds. He stressed that this was not National Assistance, but theirs as of right, just as were family allowances.

Sir HUGH LINSTEAD, in the course of the debate, said that from letters he had received as secretary of the Pharmaceutical Society it was clear that many pharmacists believed that some of the charges would create hardships for deserving patients, and that some doctors to help patients would prescribe one item for two members of a family or omit a desirable item under pressure from the patient. Another effect would be self-medication. A general criticism was that doctor and patient were in a sort of conspiracy to defeat charges. Sir Hugh went on to say that his personal fear was hardship for the fringe group of people just above the National Assistance level.

Turning to the future he said that with every possible economy the drug bill would continue to rise. The only person who could control this section of the health service was the prescriber. Doctors must be kept in touch with modern methods of prescribing by other means than through the representations of the manufacturing houses. As long as the principle that the doctor was to be free to prescribe whatever he believed his patient needed was safeguarded, his knowledge and his judgment were the main things that the Minister must rely on for economy. The patient could do little to control prescribing. For that reason Sir Hugh regretted that the patient should have to pay for increased costs over which he had virtually no control.

Mr. ENOCH POWELL, the Minister of Health, in winding up the debate, suggested that the charges had not proved a barrier to treatment, since the number of prescriptions dispensed in

1. H.M. Stationery Office, 6*d.*
2. S.I. 1961, no. 182.
3. Mair, A., Mair, G. B., Taylor, A. *Brit. med. J.* 1960, ii, 1442.

1960–61 was greater than in the last year before the 1956 charge. The Opposition apparently believed that it was more important to keep the present level of charges, which were not withholding the benefits of the N.H.S. from anyone, rather than have £12 million or £13 million for expenditure on essential purposes. Neither the National Health Service, nor the society in which it existed, stood still. They were both living, changing things reaching out to new aims as people were able to meet old needs for themselves.

Suicide Bill

On Feb. 14 Viscount KILMUIR, the Lord Chancellor, introduced in the House of Lords this short measure amending the law relating to suicide in England and Wales. If it is passed, suicide will cease to be a crime. Anyone who is convicted of complicity in another's suicide will be liable to a prison sentence of not more than 14 years, but proceedings will not usually be instituted except with the consent of the Director of Public Prosecutions.

Social Problems and Immigration

On Feb. 17 Mr. CYRIL OSBORNE moved that the Government should take powers to control immigration from the Commonwealth into this country and to require every immigrant to show proof of a guaranteed job and accommodation, a clean bill of health, a clear criminal record, and a cash deposit for their return fare. He excluded from the motion students and professional workers who came on limited visits. The West Indians, he considered, the major section of this dangerous and delicate problem. In 1953, 2000 came to this country, last year 50,000 came. There were now about 300,000 coloured people in this country, and in his view they were causing grave social difficulties in Birmingham, parts of London, and other industrial cities. Many of these immigrants could live better here on the dole and our social services than they could by working hard in their own countries.

Mr. DAVID RENTON, joint under-secretary of State for the Home Department, said that the Government had been watching closely the increasing immigration from the Commonwealth and considered that generally immigrants did not create new social problems, but increased existing ones, sometimes seriously, especially in areas where they concentrated. The danger to the nation's health from their presence was, so far, not serious. Though large numbers of newcomers had strained the local health services of some areas, there was no evidence that in any district the situation had got out of hand.

It was undeniable that some existing social problems might worsen if immigration were to continue at last year's rate. The Government had been anxiously considering what could be done. Administrative action by the overseas Governments concerned could help. At home, local authorities needed more powers if they were to intervene to improve the squalid conditions in houses in multi-occupation. But the United Kingdom could not be considered in isolation. It was the historic right of every British subject to enter and stay in this country, which was the focal part of the Commonwealth. Even to impose conditions, such as a clean bill of health, would be administratively difficult. India and Pakistan had already said that they had not the facilities, the equipment, or the staff to check the health of intending immigrants. No doubt the same was true of the West Indies. It would have to be done at our own ports, and this would mean installing at each a complete range of diagnostic equipment and requiring each immigrant to undergo a full-scale medical examination. There were of course already powers to deal with obvious infections at the ports. The Government were considering the matter with great care and some concern, but they had not come to any conclusion. Meanwhile he suggested that the motion should be withdrawn and Mr. OSBORNE assented.

QUESTION TIME

Homicide Act

Commander J. S. KERANS asked the Home Secretary whether, in view of the increased number of murders in recent weeks, he would consider the revision of the Homicide Act 1957.—Mr. R. A. BUTLER replied: I am not convinced that any amendment of the Homicide Act would be appropriate at present. Taking statistics between set years, there was not a great increase in the murder-rate in 1957–60, for example, and 1953–55.

Mr. GRESHAM COOKE: Will the Minister bear in mind that between Dec. 11 and the end of January 17 women and girls have been murdered, the majority of whom were subject to sexual attacks? There is a very strong feeling that the Homicide Act should be now amended to restore the deterrent of capital punishment for sexual attacks.—Mr. BUTLER: I am very conscious of the deep anxiety in relation to sexual crime. I cannot accept the exact figures of my hon. Friend, only for the reason that I am having the whole of these matters carefully analysed by my research unit. When I am in a position to give the figures exactly, I will do so. Nevertheless, we must not rely on figures. We must appreciate that there is a great anxiety. The only thing I am not convinced of is the method suggested by my hon. Friend to cure this disagreeable state of affairs.

Mr. ERIC FLETCHER: There is undoubted dissatisfaction throughout the country about the operation of the Act, both on the part of those who believe in capital punishment and on the part of those who believe in its abolition. How long does the Home Secretary think that this unsatisfactory state of affairs ought to continue before the Act is revised?—Mr. BUTLER: I used the expression "at present". I think that an act of statesmanship is to give an opportunity to see how something is working out. The few years in which the Act has been in operation have not yet given us quite a full enough idea. There are deep divisions of opinion in the House, which are not governed by party considerations, about what should be done about the Act. I am aware of most of these divisions, and I only hope that they are fully understood in the country where they are largely shared.

Medicine and the Law

Void for Want of Consent

A PETITIONER, aged 30, suing by his mother as next friend, sought a decree of nullity of marriage on the grounds that at the time of the marriage ceremony in August, 1959, he was (i) incapable of understanding the nature of the marriage contract; or (ii) of unsound mind; or (iii) suffering from mental disorder within the meaning of the Mental Health Act 1959, so as to be unfitted for marriage and the procreation of children. The suit was uncontested.

Dr. T. C. Wilson, of Alton, Hants, gave evidence that he had attended the petitioner since 1947, that he suffered from Friedreich's ataxia, involving muscular atrophy and progressive paralysis, that he had the mentality of a child of five, and that he would be incapable of understanding what was involved in entering into marriage. Mr. Frank Cook, F.R.C.S., medical inspector appointed by the court to examine the petitioner, agreed with Dr. Wilson's evidence on the petitioner's physical and mental condition.

Mr. Justice KARMINSKI said that he was satisfied on the evidence that the petitioner could not have understood the nature of the marriage to which he was a party. Accordingly, the ceremony of marriage was void for want of consent. Although the evidence established the two other grounds alleged in the petition, which rendered the marriage voidable only, and not void, these did not arise for consideration in view of the fact that the first ground, which rendered the marriage void *ab initio*, had been proved. There would be a decree *nisi* of nullity.

Lee *v.* Lee (orse. Shearman)—*Probate, Divorce, & Admiralty Division*: Karminski, J. Feb. 10, 1961. Counsel and solicitors: C. R. Beddington (Stevens & Bolton, Farnham).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

February may not, at first sight, seem the most attractive month for picnics; but in our Northern climes we are nothing if not opportunists. The combined influence of a Saturday morning off, a wife convalescent from influenza and children from measles, and the welcome appearance of the sun, made us all eager to seize the opportunity of a day in the country. The day's menus were rapidly reorganised to provide for a picnic tea at lunch-time, to be followed by lunch at tea-time on return; the car was quickly loaded with ground-sheet, wellingtons, scarves, and rugs, and off we went.

The usual question "Where shall we go?" brought the usual answers—"By a river" "To the hills", "The woods", and "Near a railway line". The problem was happily solved when we arrived at one of our favourite spots, on a river-bank, with a railway on the other side, a not too distant view of the hills, and two trees in the immediate foreground. The river was full and fast, so there were not many stones to be thrown; perhaps as well, for a cold and gusty wind was whipping the tops off the little waves in the swollen river, driving heavy squalls of rain across the sky, and tossing the sea-gulls—twenty miles inland—like scraps of paper. So we picnicked in the car and watched a rainbow and the trains. Afterwards, farther on among the hills, we saw hazel-catkins and chestnut-buds, hillside streams in gushing spate, and the clean new greens of the fields and fells.

We were luckier this year than last, when a February visit to a hospital across the Pennines was the occasion of another family outing. Deceived by early sunshine, we promised ourselves a picnic lunch at the top of Hartside, where, after a long slow climb, there is (on a clear day) a wonderful panorama of the purple peaks of Lakeland, before the road plunges down in hair-raising hairpins to the Valley of the Eden. Lured by this prospect we swept past several likely stopping-places, with growing protests from two hungry children. When we got there the clouds were down to ground-level, and we had no view beyond a few mournful sheep, their dirty fleeces parted to show the cleaner wool underneath by a wind so strong that it twice removed the tea-pot lid before I could get it into the car. We may choose some odd times and places for our outings, but at least we don't get sand in the sandwiches.

* * *

I had a letter the other day from my old friend Dr. Anon Todd. He writes: "While I was naturally gratified at the publicity *The Lancet* gave to the important contribution on the ætiology of lung cancer made by my cousin Sweeney, I thought that they could with advantage have compared his diagnostic techniques with the cruder methods of our contemporaries. As you will recall, he used direct tracheoscopy, which is always so much quicker and more certain than modern bronchoscopy; he observed the cilia while they were still active and did not need to theorise about them; and he eschewed 'mere statistics', though of course in his day meres were a haunt of the poets (and their ladies) and not of the measurers".

* * *

The circular about hospital building operations didn't exactly catch us unawares at the regional board, but it has certainly caused a good deal of extra work in the last week or two. When my chief asked me to list the needs of my little bit of the region for the next ten years, I scribbled furiously at intervals for several days. Then, the last new hospital neatly allocated, I got my new secretary to help me with the list. I thought she was managing it all very nicely; but as we totted up the millions at the end, she asked (without a trace of irony in her voice), "Are these pounds or years?"

* * *

Riding scooter to hospital one morning; see man and police officer bending over pedestrian lying in road—head injuries. Head injuries? Sudden inspiration, present occupation, excited exclamation, spirit of cooperation, lure of adulation—scooter retardation noisy and wild. Soul aflame professional zeal, sense of vocation, visions brief and glowing—Lister, Sir John Moore, Grace Darling, Royal Humane Society Medal; racing thoughts a little muddled perhaps but I'm on home ground, this is my specialty; mind clears in flash, I know what to do. Prepare tactful, assured, clipped speech for coming assumption control situation.

Bounce confident, calm, visibly inflated up to my patient and attendants; small crowd gathered now; recitation prepared lines, clear-voiced, rather high but no fluffing, crowd stares: "Good morning, I think I can be of some use, I'm a medical student, just done head and neck".

Man bending over victim speaks, hardly turning head. "I'm qualified; I've done the lot."

* * *

I am a collector: by this I mean that I find it difficult to throw things away. Our cellars and basements have never been large enough to hold the things which I consider to be of great value. I hoard boxes, both wooden and cardboard, of all sizes. Each year I collect a crate of string. But when we are moving, I come into my own. From my cellar, boxes are brought "just right for the doll's house, the sewing-machine, or the pram". String and rope? No shortage whatever. Like an old quartermaster, I take pride in being able to provide for every need. Some of my more particular treasures have to be protected against the destructive urge which seems to accompany a move. Few people appreciate the intrinsic value of my length of lead-piping. True, a travelling salesman once offered me a year's subscription to the *Family Herald* in exchange for it, but by and large the necessity for moving a piece of real lead is not appreciated.

I do not particularly dislike the business of moving house. Usually I look after the packing of the china and glass. I sit in the cellar carefully wrapping things in newspaper. *The Guardian* of November, 1958: that was the time of our last move. *The New York Times* and *The Moncton Record*: these we bought on our last vacation; I never did have time to read them. *The Straits Times*? But I have not been in Singapore since 1947; surely I cannot have kept it that long? Yes, I remember now why I kept it—a most interesting issue! "Lunchtime already? Well, I have got some of the things packed." It is rather a slow job. We must face it. I am probably at my best as a provider of materials for other people's packing. I am a quartermaster, not an executive.

* * *

Last week I wrote the following letter about a patient whom I saw in a psychiatric outpatient clinic, referred because of depression.

Dear Dr. X,

re: Miss L—— M—— Age 26 yrs.

This patient offers the history of a normal childhood and upbringing followed by an uneventful life without any serious illnesses until the series of events which began last September.

First, she was found to have a gum infection and referred to the A—— B—— Hospital, to which she has so far paid nine visits and where she still has to attend.

Secondly, she developed eye symptoms and was found to have bilateral meibomian cysts, requiring excision at the C—— D—— Hospital. There, she was found to be slightly shortsighted, and glasses were prescribed.

Thirdly, while under treatment at the above hospitals, she complained of tiredness and she was also referred to the E—— F—— Hospital where mild anæmia was diagnosed. Oral iron was prescribed and she was told to return for serial blood tests.

Last week she attended outpatients at three different hospitals. If she also attends here, she will then be on the books of four hospitals, come to regard herself as being "under a psychiatrist", and thus be encouraged to develop what is already an iatrogenic anxiety state.

I have discussed things with the patient and with her mother and told her that as soon as her gum infection is cleared up, and her anæmia treated, there is no reason why she should not be completely well. And I have told her, further, that she does not need psychiatric treatment. After all, she would be more likely to need it if she had failed to be anxious about this sequence of events.

Yours sincerely,

Y. Z.

Any fisherman will spot at once that here is that rare fish—the one that got away.

Letters to the Editor

SURGEON AND ENGINEER

SIR,—Your annotation (Feb. 11) on the need for cooperation between surgeons and engineers leaves this matter as vague at the end as at the beginning. This is because you fall into the common error of believing that "the initiative must come from surgeons who are far-sighted enough to appreciate the full resources of present-day mechanical engineering, metallurgy, and electronics."

In my view the failure of British surgeons and engineers to cooperate lies with the engineers. The British Orthopædic Association has a remarkably large number of fellows and members with natural mechanical talents who are doing their utmost to teach themselves engineering theory. Almost daily the orthopædic surgeon is endeavouring to bring his technical problems before engineers; but only if he happens to have unusual creative mechanical talents, and persistence and tenacity, and if he is not put off by a cool reception given to his ideas, will he get anywhere.

The failure of engineers to cooperate positively with surgeons is easily explained. While they frequently show good will at the start of a project, this field simply does not offer a career for a first-class engineer. The best a British university department of engineering can offer is occasional spare-time help from a junior lecturer whose work is overshadowed by the preparation of his own thesis. The tendency is for the engineer to feel himself to be a "stooge" for the surgeon. In Sweden they are more realistic: for example, the University of Uppsala pays a salary which makes it worth while for a senior engineer from the Institute of Technology in Stockholm to supervise work done in the biomechanical laboratory for one whole day a week. It is possible for a senior engineer to do this because his engineering career is to some extent already determined. To sum up, it is purely a matter of paying adequately for these services.

Manchester. JOHN CHARNLEY.

SIR,—Your annotation raises an issue of considerable importance for the further development of British surgery and medicine—the necessity for increasing cooperation between doctors and engineers. The need for exchanging ideas between the two disciplines was recognised by the formation, in October, 1960, of the Biological Engineering Society.

At present, several groups can work on the same idea—for example, a heart-lung machine. Each believes that its approach is best. Eventually the most suitable apparatus will emerge. It would be undesirable if after the creation of a central medical-engineering body, all ideas were to be scrutinised by a committee of "experts". It is essential for the stimulus of competitive endeavour to be retained. It may be that an organisation modelled on the lines of the American Dental Association's laboratory in the Bureau of Standards in Washington would be more suitable. This organisation in the Bureau of Standards has access to other laboratories in the Bureau. It tests materials submitted to it and publishes specifications for dental products. It engages both in applied and fundamental research. The critical examination by a similar organisation of materials and equipment used internally and externally in surgical and medical practice would help the doctor and benefit the patient. The British Standards Institution is fulfilling a most useful function through its various committees which consider devices in general use. But it does not have its own research facilities—often needed to obtain information to create a standard.

The body your annotation proposes could:

(1) provide reference library facilities;

(2) put research-workers in touch with others all over the world working in their specialty;

(3) provide an appreciation and testing service for devices produced by individuals or research groups;

(4) provide facilities for research either on various problems of its own, or requested, for example, by the British Standards Institution, the Ministry of Health, individual surgeons, or engineers.

It should be autonomous, financed by the Government and industry, with a management committee with both academic and industrial representatives. Such a body would not preclude the need for engineers to work full-time with medical staff, in particular institutes and hospitals, to study such problems as prostheses or breathing equipment.

Department of Biomechanics
and Surgical Materials,
Institute of Orthopædics,
Royal National Orthopædic Hospital,
Stanmore, Middlesex. JOHN T. SCALES.

SKELETAL FLUOROSIS

SIR,—Dr. Holman (Feb. 18) seems to think that because 8 out of the 46 cases in the series described by Prof. Amarjit Singh and his colleagues (Jan. 28) with evidence of skeletal fluorosis did not also have signs of dental fluorosis, this invalidates the well-established contention that dental fluorosis is a sensitive indicator of potentially toxic levels of fluoride in the water supply.

This conclusion is wrong for two reasons:

(*a*) It is not at all clear from the original paper that these 8 cases had resided "in the endemic area while their permanent teeth were erupting". If in fact they emigrated into the area (or changed their water-supply) after the age of, say, 10 years, the absence of dental fluorosis is quite irrelevant to the point at issue. The 38 other cases of skeletal fluorosis that are specifically referred to as having lived in the area at the material time all had "fairly advanced" dental fluorosis.

(*b*) In any case 90% of the population of the area *did* have dental changes clearly indicating that the fluoride level in the water was too high.

It should further be noted that in the extreme conditions of a tropical climate with some of the population "abjectly poor" and the level in water-supplies as high as 14 p.p.m., a 90% dental fluorosis-rate was associated with only a 2·7% prevalence of skeletal fluorosis. In a survey of 170,000 radiographs of residents of Texas and Oklahoma where conditions would be much closer to our own than would be those in the Punjab, Stevenson and Watson [1] found that *symptomless* osteosclerosis did not occur even in old people unless there was at least 4 p.p.m. of fluoride in the water-supply.

Anglesey. G. WYNNE GRIFFITH.

COLLEGE OR DIVISION?

SIR,—The first annotation in your issue of Feb. 18 will be read with interest by many, so I write to point out a fallacious argument you repeat in your reporting: ". . . but, including the votes of those willing to accept a majority decision and of those with no strong preference, 681 were prepared to support a faculty, compared with 669 prepared to support an independent college."

Like must be compared with like. The A votes you quote are comparable being primary votes, ". . . 415 favoured the establishment of an independent college, while 350 favoured the creation of a faculty within the Royal College of Physicians." The B, or secondary votes you would add to give the figure of 681 (for a faculty) and 669 (for an independent college) cannot be compared. Many exercising the A vote deliberately refrained from exercising the B vote because they disagreed with the complex format of the voting paper, and I am told other members were actively dissuaded from casting their B

1. Stevenson, C. A., Watson, A. R. *Amer. J. Roentgenol.* 1957, **78**, 13.

vote if they were known to be exercising their A vote in favour of an associated faculty or division.

The main point, however, one which you omit, is that 765 out of 838 members voting want some form of organisation in pathology in the immediate future. On a previous occasion voting was 83% in favour of an independent college. Many pathologists in regional hospitals hold the view that the past decade has been wasted in needlessly fruitless discussions, and that their desires and their needs have been neither appreciated nor met by certain seniors, either through their inability or their unwillingness to march with the times.

Most will agree with your contention " that the function of colleges is to integrate the profession rather than fragment it ". This would be one of the chief objects of an independent college of pathologists—the integration of the several newer divisions with the older discipline of pathology. The Pathological Society with its senior standing and great tradition could and should play an important part in the future of pathology. There is little reason today for the Society to decline to be associated with the mechanics of professional existence when these affect the great majority of pathologists. It is to be hoped that the Society will not fail to accept the challenge of this time of change and that the Society's contribution of wise statesmanship will be accompanied by an equal measure of catholic outlook, foresight in planning, and courage in translating plans into action.

North Middlesex Hospital, London, N.18. J. F. HEGGIE.

SHINGLES AND CHICKENPOX

SIR,—As suggested in a recent annotation,[1] a convincing history of contact between patients with herpes zoster and varicella—children or adults—though usually sought is seldom obtained. In the last fifty cases of herpes zoster ophthalmicus which I have seen a possible positive contact history was forthcoming in only two:

One man contracted herpes zoster while living in the same house as children who had chickenpox, and another elderly man from Yorkshire while visiting a grandson who was recovering from chickenpox in London. Within 2 weeks the second man had severe herpes zoster ophthalmicus involving both first and second branches of the nerve. In due course he returned to Yorkshire, and some days later a grandson there developed chickenpox, and another grandson virus pneumonia.

I agree with Colonel Foster [2] and Dr. Lawson [3] that the relationship is not necessarily indirect. Cheeseman [4] found in 1935–39, in various types of schools, that the proportion of cases of herpes zoster with a previous history of chickenpox averaged 85%. From this it seems that an attack of chickenpox does not necessarily confer immunity from herpes zoster. Considering that both conditions are relatively common, one might expect them to arise simultaneously more often than reports suggest. In the following case both conditions were seen in the same patient:

A man, aged 62, noticed vesicles on the left side of his forehead on Sept. 9, 1960. He had no malaise or other symptoms; and no history of chickenpox, or chickenpox contact, could be elicited. 3 days later he was admitted to hospital, where the diagnosis of herpes zoster ophthalmicus was confirmed (see figure). On Sept. 23 a vesicular rash appeared on both sides of his forehead, nose, face, chest, arms, back, legs, and thighs. A blood-count showed that the white cells were 6200 per c.mm. (polymorphs 47%, eosinophils 2%, monocytes 4%, and lymphocytes 47%), and that abnormal cells of virus-infection type were present. The erythrocyte-sedimentation rate (Wintrobe) was 15 mm. in the 1st hour. The patient was transferred to an isolation hospital after the diagnosis of chickenpox was confirmed.

Royal Eye Hospital, London, S.E.1. A. J. CAMERON.

1. *Lancet*, 1960, ii, 1019.
2. Foster, H. *ibid.* p. 1253.
3. Lawson, G. *ibid.* p. 1349.
4. Cheeseman, E. A. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1950, no. 271, 45.

RHESUS-TYPING IN ACQUIRED HÆMOLYTIC ANÆMIA

SIR,—Dr. Weiner and Dr. Nussey (Feb. 4) point out the danger of relying on papainised sera for grouping patients known to have acquired hæmolytic anæmia, or for grouping babies with hæmolytic disease of the newborn. They recommend the use of saline agglutinating antibody in rhesus typing.

In hæmolytic disease of the newborn is there not the danger that the red-cell receptors may be " blocked " with incomplete antibody? If they are would the cells still be agglutinated with saline agglutinating antibody?

Basingstoke. D. J. MCLOUGHLIN.
Southampton. R. D. MACKENZIE.

ATHEROSCLEROSIS AND CORONARY THROMBOSIS

SIR,—In their letter (Feb. 17) Mr. Howard and Dr. Gresham have misinterpreted our paper (Jan. 28). As their comments can only add further confusion to this complex subject we would like to reply to some of the points they raise.

In reinterpreting our figures they select from our results those figures which fit their hypothesis and ignore those which do not. Thus they point out that of 75 arteries in each age-group there were 18 occluded by recent thrombus in the youngest, but only 11 and 10 in the two older groups. Stating that this means " that the pattern of heart-disease differs in younger men " they conveniently ignore our figures for old and recent occlusions combined, which add up to 29, 34, and 30 arteries in the three age-groups (table IV in our paper).

It is surely not a very profound observation that in younger subjects recent lesions are more numerous than in older subjects in whom many of the lesions present are of longer duration. If this is what Howard and Gresham mean by " a different pattern of heart-disease ", then we cannot agree that it represents any essential difference in pathogenesis.

The facts are that in our cases there were no qualitative differences between the three age-groups in respect of site and distribution of lesions, gross and microscopic appearances of the arteries, and effects on the myocardium. In respect of extent of confluent atherosclerosis and frequency of occlusions there is not even any significant quantitative difference. Mr. Howard and Dr. Gresham prophesy that if we had studied subjects aged 60–80 years the differences would have been " even more striking ". Unwilling to enter these realms of prophecy we have surveyed the gross findings in 50 consecutive cases at this age. The presence of recent thrombus was recognised in 28 of them, which can hardly fit Dr. Gresham's definition of " rare " (defined by the *Oxford English Dictionary* as " exceptional " or " seldom found "). When Mr. Howard and Dr. Gresham speak of " silting up the fine branches " we find ourselves unable to follow their meaning. In our cases we never observed stenosis of fine branches in the absence of lesions in the major vessels; and the classic studies of Duguid [1] and Morgan [2] now leave no doubt that stenotic lesions are in fact the end-results of mural or occlusive thrombosis. It is not surprising if these end-results are more frequent in those who have lived longest with the disease.

We do not disagree with Mr. Howard and Dr. Gresham about the importance of experimental work in isolating

1. Duguid, J. B. *J. Path. Bact.* 1946, **58**, 207.
2. Morgan, A. D. The Pathogenesis of Coronary Occlusion. Oxford, 1956.

and studying the different factors which may be involved. We must, however, repeat that in the cases we have studied recent occlusive thrombosis was observed only at sites of severe atherosclerotic stenosis and that the disease in the young did not differ essentially from that in the older age-groups.

T. CRAWFORD
D. DEXTER
R. DONALD TEARE.

St. George's Hospital Medical School, London, S.W.1.

SIR,—Dr. Gresham and Mr. Howard [1] described experiments with rats which led them to conclude that (1) atherosclerosis and thrombosis are not necessarily related; and (2) plasma-cholesterol is not necessarily an index of atherosclerosis.

While each of these premises may be correct, I believe the experimental model upon which the premises were based is inappropriate; and the authors inaccurately attribute its development to Thomas and Hartroft.[2] A summary of the atherogenic regimens fed to rats may help to dispel a widespread misconception that the myocardial infarctions produced in rats resemble those in man.

The hypercholesteræmic effect of feeding certain bile acids was described by Schönheimer in 1924.[3] This observation was often repeated (see, for example, the review by Member et al.[4]). The latter authors then showed that the hypercholesteræmic effect was limited to cholic acid and its peptides. In 1952 Page and Brown [5] combined thyroid ablation with cholesterol and cholic-acid feeding to induce atherosclerosis in rats. They were influenced in these studies by the work of Friedman and Byers on the influence of cholate on cholesterol metabolism.[6] Page and Brown did not consider the arterial lesions they produced to be atherosclerosis, since they saw no evidence of a tissue reaction to the intimal lipid infiltration. Meanwhile Wissler [7] and Malinow and his coworkers [8] by combining cholesterol-feeding regimens and methylthiouracil-induced hypothyroidism with hypertension and perinephritis respectively had described proliferative lesions which looked authentic.

In 1956 Fillios and his colleagues [9] carried the work another step by showing that rats kept on a regimen of cholesterol, cholate, and thiouracil developed gross aortic lesions resembling atherosclerosis in man. The dietary fat was corn-oil, the serum-cholesterol levels were 500–2500 mg. per 100 ml., and the lesions appeared in as little as 30 days. No infarctions were seen. These workers were impressed by the toxicity of the regimen. Even adult rats lost weight; and the mortality was high. This toxicity led them to conclude that this rat model was inappropriate for experimental use.

Subsequently Thomas and Hartroft [2] adopted the technique, and by substituting butter-fat for the seed-oils produced even more remarkable lipæmia and toxicity. These authors began from the finding that since experimental atherosclerosis rarely progressed to myocardial infarction, the factors responsible for atheroma might not be identical with those responsible for the complications. Thomas has described the effect of diets with thiouracil, cholate, cholesterol, and several kinds of fat.[10] The animals gained no weight, their mortality was very high, and the levels of serum-cholesterol were also high (3360 mg. per 100 ml. in the group fed butter). The remarkable observation was made that animals with infarctions survived as long as those without. Many animals were found with "infarctions" of the visceral organs. The other pertinent observation was that thrombotic occlusions could not be related to specific local vascular lesions—the occlusions were *not* at the sites of plaque-formation.

Now the question is, are these lesions relevant? Are these experimental "infarctions" related in any causal way to those in man? I think not. I believe the most plausible explanation of these experimental infarcts is related to the viscosity and obstruction to flow produced by the intense and unique lipæmia produced in the rat. Obstructive thrombosis without atherosclerosis is thus a mechanical phenomenon and irrelevant to the problem in man. This phenomenon, with the "atherosclerosis" produced by choline deficiency in rats,[11] remains a laboratory curiosity sometimes useful for promoting lipotropic agents.

Vanderbilt University School of Medicine, Nashville, Tennessee. G. V. MANN.

1. Gresham, G. A., Howard, A. N. *Lancet*, 1960, ii, 527.
2. Thomas, W. A., Hartroft, W. S. *Circulation*, 1959, **19**, 65.
3. Schönheimer, R. *Biochem. Z.* 1924, **147**, 258.
4. Member, S., Bruger, M., Oppenheim, E. *Arch. Path. (Lab. Med.)* 1944, **38**, 210.
5. Page, I. H., Brown, H. B. *Circulation*, 1952, **6**, 681.
6. Friedman, M., Byers, S. *Amer. J. Physiol.* 1952, **168**, 292.
7. Wissler, R. W. *Proc. Chicago Inst. Med.* 1952, **19**, 79.
8. Malinow, M. R., Hojman, D., Pellegrino, A. *Act. cardiol., Brux.* 1954, **9**, 480.
9. Fillios, L. C., Andrus, S. B., Mann, G. V., Stare, F. J. *J. exp. Med.* 1956, **104**, 539.
10. Thomas, W. A. *Bull. N.Y. Acad. Med.* 1960, **36**, 555.
11. Wilgram, G. F., Hartroft, W. S., Best, C. H. *Brit. med. J.* 1954, ii, 1.

TREATMENT OF HOMOSEXUALITY

SIR,—I have known a well-qualified medical analyst who claimed to be able to change *every* homosexual to a happy heterosexual state. I also know analysts who believe that homosexuals cannot be changed, and who confine their efforts to getting the patient to accept his homosexual state and live with it. There are still others who believe that *most* homosexuals can be changed. Have we, however, considered how unfair this state of affairs is to our patients? It might make all the difference to the health and happiness of a patient if he is sent to a member of group 1, 2, or 3 for treatment.

The Medical Research Council might agree to support a research scheme which might help to eradicate a possible injustice to some patients.

London, W.1. JOSHUA BIERER.

THE OTHER PART OF MEDICINE

SIR,—It is interesting to note some formal analogues to the practical approach developed by Dr. Balint in his paper (Jan. 7).

Dr. Balint's "involvement in the therapeutic relationship" recalls the suggestions, for example, of Pask [12] who speaks of the "cybernetician", faced with an "exceedingly complex system", as a man who "obtains his experience not by mere observation, but by interaction . . . he builds up a common language in terms of which he and the system may interact and form a macro-system . . . the common language is a language of participants, unsuitable for expressing logical assertions . . . we distinguish a scientific observer who minimises interaction and a participant observer who in general tries to maximise his interaction . . ."

Minsky [13] also seems to envisage the possibility of establishing communication with very complex systems through a special language which will leave the system autonomous, rather than acting directly on the system in a crudely manipulative fashion.

Dr. Balint's dichotomy of "precision" and "integration" is perhaps mirrored by a half-jocular proposal due to Cronbach,[14] who suggested that it is worth sacrificing fidelity ("precision") to obtain optimal bandwidth ("integration"). For cases where well-defined measures are available, rigorous statements have been formulated by Hartley, Shannon, Gabor, Mackay, and others,[15] these formulations being broadly comparable to Heisenberg's principle in physical science. A familiar application is in radio-receivers, which may be designed for fidelity or selectivity, but not for both simultaneously.

12. Pask, G. *Cybernetica*, 1958, **1**, 155.
13. Minsky, M. L. *in* Mechanisation of Thought Processes; p. 14. London, 1959. (Nat. Phys. Lab. Symp. no. 10.)
14. Cronbach, L. J. *Psychometrika*, 1954, **19**, 263.
15. Cherry, C. On Human Communication. London, 1957.

Mackay [16] remarks on the necessity for discriminating among the range of attitudes betwen the "precipitate confidence of the over-speculative and the impotent caution of the rigid logician". A reasonable solution to this problem, he says, is one of the marks of a man of intellect—to show true intellect, one must know when the occasion demands a lowering of the thresholds of evidence (and to this second-order problem, there is, presumably, no absolute solution).

Gartloch Hospital,
Gartcosh, Glasgow. J. B. COLLINSON.

THE WRIGHT NEBULISER

SIR,—I am indebted to Mr. Daniels for his letter (Feb. 11) about my nebuliser, because I have been trying for years to persuade the makers to supply a coloured bottle, so far unsuccessfully.

As mentioned in my original description [17] the bottle is a standard 'Universal' container which is cheap and readily available anywhere; and we hoped that when the nebuliser was being made in quantity it would be easy to persuade a glass manufacturer to make amber bottles from the same mould.

Unfortunately it has proved impossible so far to interest any manufacturer in an order for less than 10,000 coloured bottles, even if the design is standard.

Although the nebuliser is widely used, it is unlikely ever to be sold in these quantities, so that unless you, Sir, can your use influence to persuade a glass manufacturer to be swayed by other than purely commercial considerations, it looks as though users impressed by the other advantages will have to put up with the disadvantages of a clear bottle.

Meanwhile, I would suggest that no solution be kept for 3 days in the nebuliser. It is better practice to put only the daily requirement in the bottle and discard any residue. In addition, it is a simple matter to slip over the bottle a cardboard sleeve, or even to persuade a grateful patient to knit a little jacket for it!

National Institute for Medical Research,
Mill Hill,
London, N.W.7. B. M. WRIGHT.

ORAL PROGESTOGENS

SIR,—Mr. Klopper and Mr. Macnaughton (Feb. 11) gallantly attempt to instruct on the correct method of naming steroids, but unfortunately only add further to the confusion. They make no attempt to distinguish between systematic and trivial names, and indeed are themselves confused. They state, for example, that 19-*nor*testosterone is not 19-*nor*androstenolone when in fact it is one of several possible substances which this name could include.

Most steroid substances used in medicine can be related to three basic ring systems, oestrane, androstane, and pregnane, all of which are well-defined, and the use of *nor*androstane for oestrane is no more correct than the use of *dinor*pregnane for androstane.

Systematic names are based on approved ring systems with substituents added as suffices or prefices according to accepted rules (International Union of Pure and Applied Chemistry).[18] Thus the systematic name for 19-*nor*testosterone is 17β-hydroxyoestr-4-en-3-one and the substance with no oxygen at position 3 is oestr-4-en-17β-ol, not 3-desoxy-19-*nor*testosterone in which an unwanted 3-keto group is introduced in the trivial name only to be deleted by the unnecessary prefix.

Finally the term allylestrenol conveys almost all that is necessary to a chemist or to anybody who reads the list of approved names issued by the General Medical Council (Aug. 1960), where its systematic name of 17α—allyloestr-4-en-17β-ol is also given. We have undoubtedly committed an orthographical crime in dispensing with the approved diphthong, but we plead the *force majeure* of an export drive.

16. Mackay, D. M. *in* Mechanisation of Thought Processes; p. 43. London, 1959.
17. Wright, B. M. *Lancet*, 1958, ii, 24.
18. See *J. Amer. chem. Soc.*, 1960, **82**, 5577.

The remarks of Dr. Field-Richards and Mr. Snaith (Jan. 21) on the use of *nor*testosterone compounds in pregnancy are valid. Allylœstrenol is no more correctly designated as 17-allyl-3-desoxy-19-*nor*testosterone than is oestradiol as 1(10)-dehydro-19-*nor*testosterone.

Organon Laboratories, Ltd.,
Newhouse,
Lanarkshire. C. L. HEWETT
Director.

REPRINTS

SIR,—No-one would deny that there are many people who apparently feed on printed matter. Reprint collectors are well known to scientists and to librarians and it is reasonable to suspect that the requests of scientists who demand reprints of papers dealing with subjects covering different or unrelated fields are irresponsible ones.

It must be said, however, that a large part of the dissemination of scientific literature is carried on by means of the exchange of reprints. It is perhaps the best method by which scientists keep in touch with the work of their colleagues and at the same time maintain a personal collection of papers relevant to their own work.

It seems absurd to expect scientists always to be under the necessity of writing a letter whenever they need a reprint. The loss of time alone could be considerable. A polite printed card is adequate and sufficient, and provided that the receipt of the reprint is acknowledged, then surely the demands of courtesy are met. Incidentally, Dr. Farnan (Feb. 18) is wrong in supposing that the French never send reprint request cards. We frequently receive them.

Dr. Faulds (Feb. 11) mentions requests for several copies of the same reprint from one person. This practice is irritating and one which I personally would deplore; nevertheless it may well be that these requests are made by someone who is acting for an entire institute or for a whole group of research-workers and who is simply passing on these requests and thus obviating the need for several cards or letters.

It is in practice hardly possible to decide which requests for reprints are genuine and which are not; but I would suggest that any request which comes from a librarian should be sympathetically considered and that those requests should be met which come from scientists in countries where library facilities are perhaps not so abundant as our own.

In the last analysis it is surely better to waste a reprint or two rather than to risk withholding a piece of information, which notwithstanding appearances to the contrary may be genuinely sought after and truly needed.

Chester Beatty Research Institute,
London, S.W.3. DENNIS A. BRUNNING
Librarian.

SIR,—Dr. Faulds' experience (Feb. 11) is of course not unique. But the appetite for collecting reprints has been encouraged by the growing practice of some authors and of departments to order many reprints and bestow them regularly over a wide field. Surely this reprint practice is much overdone, and is an unnecessary expense which young authors should not feel necessary for the recognition of their work. There must be very few big libraries that do not stock most journals, and the excuse that the applicant is unable to obtain the journal can only rarely be valid. The reprint habit is becoming as irritating as the glossy-backed advertisements.

Dr. Faulds' former custom is surely correct, to order only a few for the bona fide applicants, and first come first served; the printed postcard can be safely ignored and consigned to the wastepaper basket.

The London Hospital,
London, E.1. D. W. C. NORTHFIELD.

SIR,—I think the answer to Dr. Faulds' inquiry has in recent years become a simple one. Provided that a large

number of photographic reproductions are not an integral part of the article, any well-found institution can make themselves a photostat copy for little more than the cost of postage.

Queen Mary's Hospital for Children, Carshalton, Surrey. DAVID LAWSON.

NIALAMIDE

SIR,—I should like to confirm the findings of Dr. Sowton (Feb. 4) that nialamide is ineffective in relieving pain.

Since preliminary reports had suggested that this drug relieves skeletal pain, I carried out a small pilot trial in patients with root pain arising from prolapsed intervertebral discs. 8 consecutive cases with root pain severe enough to require analgesics and with neurological evidence of root compression were selected. 6 cases had a cervical disc protusion with pain referred down the arm and neurological signs of compression of the seventh cervical root; 2 had lumbar disc protrusions with sciatica, 1 with compression of the fifth lumbar, and the other of the first sacral root.

The patients were asked to continue the analgesic tablets they already had, which in no case had been adequate to relieve their pain. In addition they were given nialamide, 25 mg. q.d.s. They were asked to report what change, if any, they noted in their pain and in the number of analgesic tablets required per day. No suggestion was made on the effect the new tablets might have.

During the trial-period, lasting from four to six days, no other treatment was given. At the end of the trial-period no patient reported any further relief from the addition of nialamide or reduction in analgesic requirements. 2 patients, on their own initiative, increased the dose to 50 mg. q.d.s. without any effect.

Although uncontrolled, this pilot trial would appear to indicate that nialamide is ineffective in the relief of skeletal pain.

I wish to thank Dr. P. Bauwens for permission to publish, and Dr. J. Morrison of Pfizer, Ltd., for supplies of nialamide.

Department of Physical Medicine, St. Thomas's Hospital, London, S.E.1. D. A. H. YATES.

CLOSED-CIRCUIT HALOTHANE

SIR,—Your leading article (Feb. 11) does less than justice to Marrett,[1] who was the first to show that when halothane is vaporised within a closed-circuit system there is no build-up of halothane concentration as long as the patient is breathing spontaneously. The subsequent study of the pharmacokinetics of halothane by Duncan and Raventos [2] provides an explanation for Marrett's observations; and the more recent contributions from Cardiff [3–5] present a quantitative analysis of the respiratory factors involved. But Marrett still deserves credit for making the observations that many of us failed to make.

Besides this unfortunate omission your leader makes two assertions which should be challenged.

First, it is not "clearly dangerous to apply artificial ventilation to a patient with the vaporiser inside the breathing circuit". The danger lies in the use of excessive ventilation; if the tidal and minute volumes are kept within normal limits the danger is so slight as to be negligible.

Second, your statement that when the vaporiser is placed outside the path of the patient's ventilation, ventilatory changes produce only a small effect on the inspired concentration is wrong. Moreover, although Mapleson is quoted as the authority for this statement, reference to his paper [3] will confirm that in fact the reverse is the case. I readily agree that when the vaporiser is outside the circuit the *amount* of halothane to which the patient is exposed in unit time is unaltered by changes in ventilation; but this is not the same as *concentration*. It depends, of course, on what you mean by "a small effect"; but I do not regard a three- or four-fold change in concentration as a small effect with an agent as potent as halothane.

With the vaporiser outside the closed circuit the inspired concentration of halothane cannot exceed that in the fresh gas inflow. Indeed, in practice, the difficulty of using this system is not one of overdosage but of underdosage. If the concentration of halothane vapour is restricted to not more than 4%—as with some vaporisers in current use—it is almost impossible to maintain anæsthesia for major surgery on the basal oxygen flow because the *amount* of halothane vaporised is inadequate. It is for this reason, and not for reasons of safety, that a fresh gas inflow of 1–2 litres is employed when the vaporiser is placed outside the circuit.

Department of Anæsthetics, Postgraduate Medical School, London, W.12. J. P. PAYNE.

1. Marrett, H. R. *Anæsthesia*, 1959, **14**, 28.
2. Duncan, W. A. M., Raventos, J. *Brit. J. Anæsth.* 1959, **31**, 302.
3. Mapleson, W. W. *ibid.* 1960, **32**, 298.
4. Galloon, S. *ibid.* p. 310.
5. Mushin, W. W., Galloon, S. *ibid.* p. 324.

THIACETAZONE AND ISONIAZID

SIR,—It was with a certain grim amusement that we read your leader of Feb. 11 in which you discuss the recent East African trial showing the effectiveness of this combination in patients with acute extensive pulmonary tuberculosis.[1]

As you pointed out, the risk of toxic effects prevented the full evaluation of thiacetazone in Great Britain and in the United States. Elsewhere, more probably it was the advent of isoniazid which killed interest in the thiosemicarbazones. Very few papers have been published on these compounds since 1953.

In 1954, Barry, Conalty, and Gaffney described [2] the good results obtained with a combination of isoniazid and thiacetazone (amithiozone) in experimental tuberculosis, the ability of the thiacetazone to delay the emergence of strains of tubercle bacilli resistant to isoniazid, and the great susceptibility of isoniazid-resistant bacilli to thiacetazone.

Novel antituberculosis agents were prepared [3] in these laboratories by condensing isoniazid or *p*-aminobenzalthiosemicarbazone with periodate-oxidised polysaccharides. It was shown that these substances were highly effective in animal tuberculosis.[4] A mixed polymer, known as hinconstarch, made by condensing oxidised starch with an equimolar mixture of isoniazid and the thiosemicarbazone, was shown to be effective in experimental infections caused by isoniazid-sensitive or isoniazid-resistant bacilli. In synthesising hinconstarch the aim was to produce a single acceptable compound for oral administration which would utilise the high tuberculostatic activity of isoniazid and at the same time would be slow to permit the development of isoniazid resistance. Whether or not this aim was achieved may be judged from the published results.

The results of Barry, Conalty, Counihan, and O'Brien [5] and these workers with Edward and Walsh [6] showed, in a series of 52 patients, that a daily dose of hinconstarch of 40–45 mg. per kg. was as effective as other standard regimens in pulmonary tuberculosis. Katz and his associates reported similarly.[7] Walsh and Conalty,[8] who used it in genitourinary tuberculosis,

1. *Tubercle, Lond.* 1960, **41**, 399.
2. Barry, V. C., Conalty, M. L., Gaffney, E. E. *Irish J. med. Sci.* 1954, no. 343, 299.
3. Barry, V. C., McCormick, J. E., Mitchell, P. W. D. *Proc. R. Irish Acad.* 1954, **57B**, 47.
4. Barry, V. C., Conalty, M. L., Baffney, E. E. *Brit. J. Urol.* 1955, **27**, 35.
5. Barry, V. C., Conalty, M. L., Counihan, H. E., O'Brien, B. *Amer. Rev. Tuberc.* 1956, **73**, 219.
6. Barry, V. C., Browne, N. C., Conalty, M. L., Edward, D. W., O'Brien, B., Walsh, A. J. *ibid.* 1958, **77**, 953.
7. Katz, S., Donohue, R., Hawkins, J. Trans. 16 Conf. on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1957, p. 400.
8. Walsh, A., Conalty, M. L. *Brit. J. Urol.* 1958, **30**, 25.

also found that it gave results at least as good as other anti-tuberculosis treatments and that toxic effects were conspicuously absent. O'Flynn [9] also reported good results in this type of tuberculosis. De Tavera and his colleagues [10] got good results in Filipino children aged 8 months to 14 years, the response being particularly rapid in extrapulmonary lesions.

These results suggest that hinconstarch has been for several years an obvious candidate for exhaustive investigation in human tuberculosis. It would appear to be particularly suitable for domiciliary treatment in those parts of the world where medical and hospital services are underdeveloped.

Medical Research Council of Ireland Laboratories, Trinity College, Dublin.

VINCENT C. BARRY
MICHAEL L. CONALTY.

AN AID TO THE DIAGNOSIS OF HYPOFIBRINOGENÆMIA

SIR,—In hæmorrhage associated with childbirth certain laboratory investigations are urgently necessary. If the bleeding is due to hypofibrinogenæmia the treatment is easy, prompt, and effective.

The clinician may, however, have difficulty in remembering the kinds of blood samples needed by the pathologist, or suitable containers may not be at hand: for example, blood-fibrinogen cannot be estimated on clotted blood, and oxalated blood is useless for the clot-observation test.

The outfit (see figure) I describe serves both as an aide-memoire and as a compact carrier for the containers needed. It comprises a board measuring about 14 × 10 in., with Terry clips which hold a sterile 10 ml. syringe, a sterile needle, a bijou Wintrobe (double oxalate) bottle, and two glass tubes, one measuring $3^1/_2 \times {}^1/_2$ in. and the other $4 \times {}^3/_4$ in. Directions on the board read:

Laboratory Aspects of Hæmorrhage Associated with Hypofibrinogenæmia

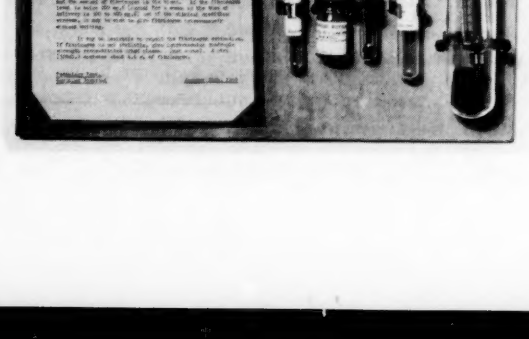
"It is suggested that if the clinician suspects hypofibrinogenæmia as being the cause of the hæmorrhage he should, in addition to carrying out all bedside investigations, contact the pathology department at once stating the investigations to be urgent.

"Alternatively, if this is impracticable or if the emergency occurs out of laboratory hours, 10 ml. of blood should be collected and the exact time noted. 1 ml. is put into the smaller tube and 2 ml. into the Wintrobe (double oxalate) bottle, which is rotated to mix. About 5 ml. is put into the larger tube. Each container is labelled with the patient's name; the smaller tube is also labelled with the exact time the blood was collected.

"The blood in the smaller tube is kept under observation. If it does not clot in 6 minutes (at most 12) this is strong evidence of severe hypofibrinogenæmia. If, however, it clots, the board carrying all the specimens should be sent to the laboratory. The small tube will be kept under observation for fibrinolysins; the Wintrobe specimen will be used for estimating fibrinogen; and the larger sample for grouping and matching blood if necessary.

"Within an hour the pathology department will send a preliminary report as to whether fibrinolysins are present, and the amount of fibrinogen in the blood. If the fibrinogen is less than 200 mg. per 100 ml. (normal for a woman at the time of delivery is 300–500 mg. per 100 ml.) it may be advisable to give fibrinogen without delay.

"Repeated estimations of fibrinogen may be necessary. If fibrinogen is not available, quadruple strength reconstituted dried plasma (not serum) may be given. 1 pint (570 ml.) of this quadruple strength contains about 4·4 g. of fibrinogen."



It is debatable whether fibrinogen should be given when the patient's blood still clots in vitro, even though the fibrinogen has fallen to 100 mg. per 100 ml. From the clinicopathologist's viewpoint there seems no doubt that to delay giving fibrinogen until the patient's blood fails to clot entails an unnecessary risk. Some degree of clotting may occur in vitro when the fibrinogen is only 100 mg. per 100 ml., and even when the fibrinogen has fallen to 46 mg. per 100 ml. a soft gelatinous clot forms.[1]

An initial normal blood fibrinogen content may be followed by a fall which can only be detected by hourly fibrinogen estimations.[2] In such circumstances I consider fibrinogen should be given when the blood-fibrinogen falls to 200 mg. per 100 ml.

The risk involved in giving fibrinogen (assuming the risk of air-embolism from frothing is avoided) may be disregarded; it is only the risk of homologous serum jaundice, and is no more than is usually entailed in giving four bottles of blood.

Worthing Hospital, Worthing, Sussex.

READ AIDIN.

VALUE OF TAPPING THE HINDWATERS IN PROLONGED PREGNANCY

SIR,—We compared the liquor from hindwaters and forewaters in 100 patients whose pregnancy exceeded 42 weeks.

Women uncertain of their dates or with an irregular menstrual cycle were excluded from our series. We tapped the forewaters before the hindwaters; no complications could be directly attributed to the use of the Drew Smythe cannula for drawing off hindwater.

The type of liquor obtained was as follows:

	No. of cases
Both forewater and hindwater clear	66
Forewater clear; blood in hindwater	23
Forewater clear; meconium in hindwater	3
Meconium in both forewater and hindwater	6
No liquor	2
	100

In 3 of the 9 patients with meconium in the liquor, it would not have been found if the forewaters alone had been tapped. The infant of one of these 3 patients died in the neonatal period, owing to intrapartum asphyxia.

Although certain risks are involved, we conclude that tapping both hindwaters and forewaters detects meconium in the liquor more accurately than tapping the forewaters alone.

We should like to thank the consultant staff at St. James', St. Mary's, and Queen Charlotte's Maternity Hospitals, London, for allowing us to operate on their cases.

St. Mary's Hospital, London, W.2.

A. C. FRASER.

Queen Charlotte's Maternity Hospital, London, W.6.

E. C. WOOD.

9. O'Flynn, J. D. *ibid.* p. 29.
10. De Tavera, M. et al. *Bull. Quezon Inst.* 1957, **4**, 189.

1. FitzGerald, T. B., Jackson, S. H. *Lancet*, 1956, i, 412.
2. Calman, R. M., Cole, P. G. *Brit. med. J.* 1960, ii, 1933.

REGISTRATION OF CAUSES OF STILLBIRTH

SIR,—Causes of stillbirth have been registered in England and Wales since Oct. 1, 1960. I would be grateful if you would allow me to comment on one particular aspect of the first three months' results which is causing some concern. During this period, out of a total of 3737 stillbirths registered, the certificate was given by a doctor in only 2360, or 63% of cases. In the remaining 37% the certificate was given by a midwife. The proportion is very little different for births at home or in hospital.

It is possible that some doctors may not be aware of the requirements of the Population (Statistics) Act 1960 which makes it obligatory on every medical practitioner who was either present at the birth of a stillborn child, or who examined the body of such a child, to give a certificate which includes a statement of the cause of death. Only if no doctor was present or examined the body may the certificate be given by a midwife.

The Registrar-General for Scotland has reported [1] that in that country midwives complete stillbirth certificates in only 0·6% of cases.

General Register Office,
London, W.C.2. M. A. HEASMAN,
Acting Chief Medical Statistician.

BRONCHIOLITIS IN INFANTS

SIR,—I obtained good results in bronchiolitis in infants (discussed in your annotation [2]) by treatment with chloramphenicol combined with an age-adjusted dose of a diuretic like chlorothiazide. The distressing symptoms (dyspnœa, grunting respirations, and rib recession) diminish within 48 hours, the temperature drops, and respiration becomes freer and more even.

Obviously bronchiolitis is an entity—probably an infection associated with some lung œdema—but more information is clearly needed about its ætiology.

Madras,
India. T. M. SUSAI.

TERSAVID IN ANGINA PECTORIS

SIR,—Dr. Murphy, Dr. Barber, and Dr. Kilpatrick (Jan. 21) are to be congratulated on their concise and conclusive paper on the effects of 'Tersavid' in angina pectoris. Their results are in keeping with the findings of Phear and Walker,[3] and with my own more modest experience of tersavid.[4]

In a preliminary study using a sequential procedure I discontinued the trial after 17 patients had been assessed. Out of 14 choices, 9 preferred the placebo as against 5 who chose tersavid. Side-effects, especially gastric, were troublesome and may well have prejudiced patients towards the placebo; in fact, 1 patient with an ulcer history had a hæmatemesis.

I was most interested in their recent conclusions, especially as my own disappointing results were obtained at the same time as their original report of improvement in 65% of their cases.[5] At the time I could not understand this at all. But I do feel that monoamine-oxidase inhibitors should not all be condemned because of the experience with one drug; other compounds should be given a controlled trial. The results of Dr. Allanby and his colleagues (Jan. 21) with nialamide, and Mackinnon et al.[6] with pheniprazine hydrochloride ('Cavodil') suggest that further work is required. Furthermore, in a condition so difficult to assess as angina, patients may be helped by a drug, but side-effects may still lead to an inconclusive or adverse opinion unless relief is dramatic. It would, therefore, be helpful in future to know in addition to bare statistical details whether there were other reasons for the patients' choice besides reduction of anginal pain. In these days of figures the final mathematical masterpiece should not make us forget clinical criteria originally chosen.

Belfast City Hospital,
Northern Ireland. A. P. GRANT.

1. Annual Report of Registrar-General for Scotland, 1959, p. 55. H.M. Stationery Office.
2. *Lancet*, 1960, ii, 806.
3. Phear, D., Walker, W. C. *Brit. med. J.* 1960, ii, 995.
4. Grant, A. P., *Irish J. med. Sci.* 1960, no. 418, 466.
5. Murphy, F. M., Barber, J. M. *Cardiologia, Basle*, 1960, **37**, suppl. 2, 117.
6. Mackinnon, J., Anderson, D. E., Howitt, G. *Brit. med. J.* 1960, i, 243.

PROTEIN-LOSING ENTEROPATHY IN THE SPRUE SYNDROME

SIR,—In his paper (Dec. 24) Dr. Parkins states that he failed to find a correlation in his patients between the serum-protein level and the fæcal excretion of radio-iodine-labelled polyvidone (^{131}I-P.V.P.). We investigated 8 patients with severe steatorrhœa of various ætiologies with Gordon's ^{131}I-P.V.P. test. In all cases with an abnormal ^{131}I-P.V.P. excretion the total serum protein and especially the serum-albumin were markedly decreased. Of course, not all the investigated patients with steatorrhœa and hypoproteinæmia displayed a pathological level of excretion of ^{131}I-P.V.P. We agree with Dr. Parkins that the protein disturbances in the sprue syndrome are complex (protein malabsorption, protein loss, and also decreased albumin synthesis by a fatty liver). Some of our findings have been published.[1 2]

P. VESIN
H. RENAULT
Hôpital Saint-Antoine, R. CATTAN.
Paris, 12e.

HÆMOLYTIC DISEASE OF THE NEWBORN

SIR,—It has been shown that some serum-proteins (antibodies in man) are transmitted from mother to fœtus in utero in primates.[3] In man the so-called "incomplete" or "albumin" antibodies can injure the fœtus in utero in contrast to the "complete" or "saline" agglutinins.

At present, hæmolytic disease of the newborn is a less important cause of infant mortality than in the past. Improved results of treatment are due, in part, to more accurate means of diagnosis by testing the blood of the mother before delivery, and to the skilful use of replacement transfusion in the newborn.

Means exist for identifying the sex and the ABO group of the unborn child by examining the amniotic fluid; it may not be long before the rhesus state of the child still in utero can be discovered by similar methods.

When all these modern methods are exploited to the full, a hard core of mothers still remain with high-titre anti-Rh agglutinins, who eventually will be delivered of an infant with hydrops, icterus gravis, or severe hæmolytic disease of the newborn. Many of those severely affected are hopeless cases or are stillborn.

There is clinical evidence that an Rh-positive fœtus may be adversely affected as early as the 27th week of pregnancy by the anti-Rh agglutinins in the mother's circulation.

According to Dr. Ludwig Mond, the only important calculation women ever have to make in their whole lives they invariably get wrong.

Fortunately, there are clinical methods which enable the antenatal age of the child to be estimated more accurately.

I would like to suggest that some of these stillbirths and hopeless cases due to Rh-sensitisation of the mother, might possibly be salvaged by treatment of the mother with steroids, in a hospital, under supervision, from, say, the 26th week of pregnancy to the 32nd or 33rd week, when the fœtus may be just viable.

It would be necessary to guard the mother against intercurrent infection with great care; and the six or seven weeks of the mother's steroid treatment might not harm the adrenals of the fœtus, though some fear that adrenal atrophy might result.

1. Vesin, P., Troupel, S., Acar, J., Renault, H., Desbuquois, G., Cattan, R. *Bull. Soc. méd. Hôp. Paris*, 1960, **76**, 261.
2. Vesin, P., Troupel, S., Acar, J., Bismuth, V., Renault, H., Cattan, R. *ibid.* p. 410.
3. Bangham, D. R., Hobbs, K. R., Tee, D. E. H. *Lancet*, 1960, ii, 1173.

If there is uncertainty as to whether steroids *can* cross the placenta from the mother to the fœtus, perhaps radioactive steroids might be administered, experimentally, to the mother just before delivery. Surely steroids should be given a trial in humans, whatever the results may have been in experimental animals.

St. Margaret's Hospital,
Epping, Essex. FRANK MARSH.

SABIN VACCINE AND COMBINED DIPHTHERIA-TETANUS-PERTUSSIS IMMUNISATION

SIR,—Our last letter [1] dealt with the response of infants to simultaneous administration of living attenuated Sabin-type vaccine and combined diphtheria-tetanus-pertussis vaccine (DI-TE-PE), and the effectiveness of the latter components. We found the immunity conferred by the diphtheria, tetanus, and pertussis antigens to be greater than in the controls, which received no Sabin vaccine.[1 2]

TABLE I—VIRUS-NEUTRALISING-ANTIBODY-TITRES AND TITRE-ELEVATIONS AGAINST TYPE 1

—	Test group Sabin + DI-TE-PE	Control group Sabin
No. of members	18	17
V.N.A.-titres†*		
<16	6	1
16	..	2
64	4	1
256	1	..
1024	7	13
Average value	426	788
Degree of titre elevation‡		
≅1×	6	2
4×	3	4
16×	2	1
64×	7	10
Average value	27×	39×

* = virus-neutralising antibody; † = reciprocal values; ‡ = immune titre: basic titre.

We have now studied the efficacy of Sabin vaccine in random groups of infants of 3 to 9 months simultaneously immunised against poliomyelitis and diphtheria, tetanus, and pertussis. Members of the test group received combined diphtheria-tetanus-pertussis vaccine, together with living attenuated poliomyelitis vaccine, while those of the control group received poliomyelitis vaccine only, as follows:

Day	*Test group*	*Controls*
1st ..	0.5 ml. DI-TE-PE and Sabin vaccine type 1	Sabin vaccine type 1
35th ..	0.5 ml. DI-TE-PE and Sabin vaccine type 3	Sabin vaccine type 3
70th ..	Sabin vaccine type 2	Sabin vaccine type 2

We determined the immunity conferred by the components of the poliomyelitis vaccine by means of virus-neutralisation tests in blood-samples taken on the 1st and on the 100th day. The assay of the serum-pairs was performed in HeLa cultures with 100 T.C.D.$_{50}$ viruses of the Mahoney (type 1), MEF$_1$ (type 2), and Saukett (type 3) strains.

TABLE II—VIRUS-NEUTRALISING-ANTIBODY-TITRES AND TITRE-ELEVATIONS AGAINST TYPE 2

—	Test group Sabin + DI-TE-PE	Control group Sabin
No. of members	19	17
V.N.A.-titres		
<16	2	4
16	1	2
64	3	..
256	..	2
1024	13	9
Average value	711	573
Degree of titre elevation		
≅1×	3	4
4×	3	2
16×	1	3
64×	12	8
Average value	42×	35×

TABLE III—VIRUS-NEUTRALISING-ANTIBODY-TITRES AND TITRE-ELEVATIONS AGAINST TYPE 3

—	Test group Sabin + DI-TE-PE	Control group Sabin
No. of members	18	17
V.N.A.-titres		
<16	4	3
16	5	2
64	2	5
256	2	2
1024	5	5
Average value	324	350
Degree of titre elevation		
≅1×	4	3
4×	7	7
16×	3	2
64×	4	5
Average value	18×	22×

We found an immune titre below 1:16 in one third of the tests on the 100th day after administering poliomyelitis vaccine type 1, while the incidence of low titres was considerably smaller in the control group. Also the average immunity, and the average increase of titre was lower in the tests than in the controls. These differences were, however, not statistically significant.

Immunological analyses performed 65 and 30 days, respectively, after the administration of type 3 and type 2 poliomyelitis vaccine proved that, compared with the controls, the efficacy both of type 3 (given together with the second dose of DI-TE-PE) and type 2 (given at a time when immunity against these three diseases reached its peak) was satisfactory. Development of immunity and the average value of titres were identical in the 2 groups receiving type 3 poliovaccine. Type 2 poliovaccine gave better results in the test group. The differences were again not statistically significant.

Summarising the results of these and earlier investigations, we feel that the simultaneous administration of living attenuated poliomyelitis vaccine and combined diphtheria-tetanus-pertussis vaccine is a safe method both as regards immunity conferred and untoward reactions.

Institute of Microbiology,
University Medical School,
Pécs, and Human State
Institute for Serobacteriological
Production and Research,
Budapest. GÉZA KELEMEN
LAJOS RÉTHY
JÓZSEF MARÓCZI
SÁNDOR PÁCSA.

1. Réthy, L., Maróczi, J., Joó, I. *Lancet*, 1960, ii, 497.
2. Réthy, L., Maróczi, J., Joó, I. *Orv. Hétil.* 1960, **101**, 915.

RENAL TUBULAR ACIDOSIS

SIR,—In your leading article (Jan. 14) you describe the terms "fixed anions" and "fixed cations" as less correct than those commonly in use in physical chemistry, namely "proton donators" and "proton acceptors".

In my opinion the former terms, unfamiliar though they may be to physical chemists, are better suited to express the values of interest in clinical medicine—not only hydrogen-ion concentration, which is in any case always measured and referred to as such, but also the "fixed" anions (in contradistinction to the readily displaced bicarbonate), and the cations or "fixed base", i.e., substances exclusively under renal control, and therefore preferably to be dealt with as independent entities.

Ammonium chloride and sodium bicarbonate do not, as you state, respectively cause a metabolic acidosis and alkalosis only because they are proton donators or proton acceptors. This may be true in vitro; but in the living organism these effects are greatly intensified as a result of the rapid removal, through general metabolic channels, of the organic radicals involved. Excess chloride will then cause an acidosis by displacing bicarbonate, and sodium an alkalosis by extending the space left for it to occupy. The administration of ammonium chloride or sodium bicarbonate is thus, in effect, equivalent to hydrochloric acid or sodium hydroxide intake.

Athens. E. T. RAKITZIS.

Obituary

HENRY ROY DEAN

D.M. Oxon., M.D. Cantab., LL.D., F.R.C.P.

Dr. H. R. Dean, professor of pathology in the University of Cambridge, died on Feb. 13 at the age of 82. He was the last professor in Cambridge to occupy his chair without statutory retiring age, and from 1929 to 1954 he was the well-loved Master of Trinity Hall.

He was educated at Sherborne School, New College, Oxford, and St. Thomas's Hospital. After qualifying in 1904 he was elected to a demyship at Magdalen College and awarded a Salters' scholarship and a Radcliffe fellowship. After some years of research and of postgraduate study in Berlin he was appointed to the chair of pathology and bacteriology in Sheffield. Three years later he moved to the chair in Manchester, where he was also dean of the medical school.

Of his years at Manchester a colleague writes:

"Dean went to Manchester with the reputation of being a brilliant research-worker in immunity and its associated serological changes. In this field he took his place with Bordet, Muir, Browning, Wassermann, and others. The war, absence of staff, and pressure of hospital work, and the needs of post-war reconstruction, interrupted the even flow of his research and he never quite regained it. The new educational problems began to absorb his interest more and more, and he turned his immediate energies to the development and redeployment of his department. Manchester in those days had in its medical faculty such men as Elliot Smith and Stopford in anatomy, A. V. Hill in physiology, Bragg in physics, and Topley in bacteriology. It was a good place to think and work in. Dean soon attracted round him many of the up-and-coming generation of the medical school. Here at tea you might meet B. J. Ryrie, Stopford, Harry Platt, R. A. Webb, G. J. Langley, John Morley, A. F. C. Davey, P. B. Mumford, T. H. Oliver, K. V. Bailey, J. C. Bramwell, Geoffrey Jefferson, P. C. Gibson, A. H. Holmes, R. Williamson, R. M. Pearse, and others who have since made their mark in the Manchester School and elsewhere."

Walter Stoneman

The general upsurge in medical education caught Dean. He expounded his ideas for the future in a noteworthy lecture in Edinburgh and before long was invited to the chair of bacteriology at University College Hospital which he accepted. But he was never to return to London. Before he could take up the appointment he was offered the chair at Cambridge, where he passed the rest of his life. Another colleague takes up the story of the early years at Cambridge:

"When Dean went to Cambridge, the university was still collecting itself after the 1914–18 war, and the medical school was ripe for change. To medical undergraduates, the department of physiology, under the professorship of Langley, newly housed in its present building, with Joseph Barcroft and Adrian at the height of their research careers, was the most important department. By comparison, the anatomy school was badly housed and traditional in its outlook. Biochemistry, under Gowland Hopkins in the new Dunn Laboratory, was burgeoning, but to some still suspect as a mixture of unorthodox chemistry with stylised biology. Nuttall, the first great immunologist in Britain, had turned his attention to parasitology in the new Molteno Institute, with Keilin as his lieutenant. W. E. Dixon taught pharmacology with unforgetable verve.

"The department of pathology, a gloomy warren on the corner of Corn Exchange Street, was venerated by students who did their 'bugs and drugs' there in long-vacation and Easter terms. It contained the department of medicine, comprising the medical library and the room of the regius professor of physic, Sir Clifford Allbutt, magnificent in his nineties but deaf. Here the new professor of pathology, then in his early forties, soon collected a team which included E. G. D. Murray (later professor of bacteriology at McGill), R. A. Webb (later professor of pathology at the Royal Free), R. Williamson, John Mills, and some research students, among them the present president of the Royal Society and, later L. J. Witts. In two years, this team created the part II pathology tripos, the prototype of academic pathology courses in this country and still almost the only one.

"Dean, in those days, was an outstandingly good teacher; a brilliant lecturer, but better still when demonstrating and discussing in the laboratory. Physically a big man, he liked to work with big apparatus. Micro methods did not appeal to him: he was no disciple of Almroth Wright. He preferred 'boiling tubes' to test-tubes, and required his reagents to be supplied in generous bulk. The onus of this fell on H. P. Hudson, now steward in the department, whom Dean brought with him from Manchester, and who supported 'the Chief' in countless ways for so many years.

"At this stage in his career, Dean's research was breaking new ground in immunology. His work on complement, begun in Wassermann's laboratory in Berlin, brought some kind of order into an erratic and difficult topic. With Webb, he first described the optimal proportions in antigen-antibody reactions, thereby providing a concept fundamental to the subject and making possible many technical refinements of great value. With his friend Hans Zinsser of Harvard, he was among the first to enunciate the 'unitarian hypothesis' of antibodies, a commonplace now, but in those days essential to further progress. With the passage of the years, little if anything that Dean published has needed to be revised, and all of it has become incorporated into the basis of immunology. Indeed, its value is better recognised now than it was when he did it. After Nuttall, Dean was the next great British immunologist."

One of his major preoccupations was the design and building of the new pathological laboratory which was provided by Rockefeller money, and which demanded of him three years' hard labour. At the time someone asked whom he would employ as an architect. His reply was characteristic: "I don't want an architect: I want the sort of chap who builds Lancashire cotton mills!" As a colleague put it, "he would have a workshop, and he got it." By 1930 the department was established in the new building, but Dean was drawn more and more into administrative work, at the cost of his research. From the start a dominant force in the medical school, as master of Trinity Hall he was increasingly involved in general university affairs. He was vice-chancellor during the two difficult and anxious years during which the preparation of Cambridge for the part which it played in the war fell to the officers of the university and the colleges. Throughout them Dean carried great responsibilities with apparent equanimity and, though necessarily he gave less time to his department, he never ceased to control and inspire it.

He also found time for many activities outside Cambridge. He was not an original member of the Patho-

logical Society, but he early joined the small nucleus—Lorrain Smith, Muir, Ritchie, Boycott, and Stewart—whose energy and foresight saw the society through its adolescence. He served as one of the secretaries (1920–54), and as the assistant editor (1920–23). He was also a part chairman of the council of the Imperial Cancer Research Fund, and a member of the General Medical Council. Another of his interests was the welfare of laboratory technicians, and he missed no opportunity of helping the Pathology and Bacteriology Laboratory Assistants Association, and later the Institute of Medical Laboratory Technology.

E. T. C. S., to whom we are indebted for much of this memoir, adds the following personal tribute:

"Dean was a strong man whose views on right and wrong, and on rightdoers and wrongdoers, were definite and not concealed. Everyone in Cambridge in the seventeen years before the war was familiar with the sight of Dean and his bulldog of the day, walking along King's Parade. He seemed to have a real fellow-feeling for these tenacious animals. He disliked humbug, servility, and sentimentality, with the cultivated dislike of the competent latinist that he was. He was adept at discomforting those whom Sinclair Lewis described as 'the men of measured merriment', by laughing at them. His own merriment was unmeasured, unpredictable, perpetual, and most endearing. It made him both friends and enemies; he was never ashamed of either."

Another friend, J. H. D., asks "How shall I round the ending of a story . . . ?" and writes:

"The death of H. R. Dean is to many of us the ending of an epoch, of a formative period in British pathology in which he played a great part: never as an aggressive or dominating figure, nor as one seeking admiration or reputation, but rather as a benign influence productive of results which surpassed any obvious effort of output. He saw and helped to guide the emergence of pathology from something between an ancillary in clinical diagnosis, or a morphological study of diseased tissues, to a lively science with its roots in physiology, bacteriology, and biochemistry and its branches in medicine and surgery.

"He was above all a man and a leader; a great personality, whimsical, amusing, affectionate, with a huge capacity and good fellowship, as great as his bodily frame. Above all he attracted men to him. The number who owe him much as an influence in their lives, a source of wise advice, a loyal helper in the struggle for existence, and through the years an inspiration, is very great. A few days ago an old friend wrote to me: 'I owe it to him that I have had such an interesting life,' and there are many who can say the same. He trusted his staff and gave them the greatest measure of freedom in their work, and he enjoyed a loyalty which remained to the end and, indeed, seemed to grow as the light began to fail.

"There have been many photographs of Dean and there is a fine portrait of him in Trinity Hall. One of him in his later years shows the slightly quizzical expression he would wear when listening judicially to some new and rather suspect doctrine from some slightly instructed speaker. But there is one I like better, taken quite recently without his knowledge, by R. M. Fry from the laboratory window. It shows 'The Old Man' standing with his back to the observer, bareheaded, holding stick and letter case behind him, contemplating the irises in the laboratory garden. Maybe irises he had grown himself from seed; and wondering what they would be like next year. There will be no irises for him next year, but for us:

> A shadow passing through the doors at evening
> To his companion and his resting-place."

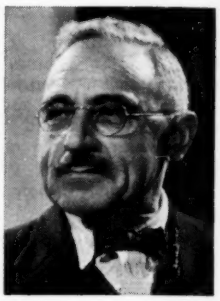
Professor Dean's wife died in 1959. He leaves a son and a daughter.

WILLY MAYER-GROSS

M.D. Heidelberg, F.R.C.P.

Professor Mayer-Gross, who died on Feb. 14 in Birmingham, made outstanding contributions to the advancement of psychiatry.

Born in the Rhineland, where his family had been established for centuries, he spent the first part of his life almost entirely in the Palatinate. After qualifying from the University of Heidelberg he obtained his doctorate in 1913 with a thesis on morbid feelings of felicity. At that time Nissl, who had succeeded Kraepelin, was the head of the Heidelberg psychiatric clinic, and he was glad to give Mayer-Gross, whose abilities were by now fully recognised, a place among the younger men on the staff of this outstanding centre. On the outbreak of war Mayer-Gross took up duty as a regimental medical officer, but in 1915 he was recalled from service in the field to help in the hospital set up in Heidelberg for the treatment of soldiers incapacitated by neurosis. After the war he returned to his academic and clinical work, and, apart from six months spent in research in a Swiss mental hospital, he remained in Heidelberg until 1933, becoming Privatdozent in 1924, and Professor Extraordinarius in 1929. He played the leading part in founding and editing *Der Nervenarzt*, and through his publications and addresses became a prominent and respected figure in German psychiatry. He was invited to take the chair of psychiatry at Groningen, but extraneous obstacles of a semi-political nature prevented it, omens of the trouble to come. With Hitler's seizure of power in 1933, and the enforcement of an edict which precluded him and so many other scholars from continuing their work, Mayer-Gross was glad to seize the opportunity to come to England on a fellowship at the Maudsley Hospital provided for the first year by the Commonwealth Fund and thereafter by the Rockefeller Foundation.



Kuenssberg

At the Maudsley Hospital his chief concern was with clinical research, but he also shared in case discussions and teaching. He and his friend Eric Guttmann worked in such close association and harmony that it was not easy to consider separately their effect on their colleagues at the Maudsley, whose affection and esteem they rapidly gained and kept. They received also much gratitude from those whose clinical grasp and research were unobtrusively furthered by them.

Mayer-Gross's direct association with the Maudsley ended in 1939 when he became director of clinical research at Crichton Royal Hospital. During the fifteen years he spent at Dumfries the clinical developments there, the fruitful research, and the admirable training provided for a succession of young psychiatrists attested the wide-ranging vitality, freshness of mind, and unselfish zest in helping younger men which were characteristic of him. When the time came for him to retire, in accordance with the rules of the National Health Service, he was far from slackening his activities. He construed this as a chance to engage in a large new undertaking, of a kind dear to his heart. There were promising developments in the Birmingham Medical School, which made the advent of a man of Mayer-Gross's great clinical experience and learning invaluable. He was appointed senior fellow in the department of experimental psychiatry then established in the university, and director of clinical research at the

newly created Uffculme Clinic. With characteristic energy and resilience, during the next five years he fostered study of the effect of hallucinogenic drugs, participated in a survey of chronic mental hospital patients, and instituted a successful day-hospital at Uffculme.

As consultant to the World Health Organisation he visited India in 1952 and 1956 to advise on the setting up of an All-India postgraduate psychiatric centre in Bangalore. He was elected F.R.C.P. in 1951, and president of the Section of Psychiatry of the Royal Society of Medicine in 1954. He delivered the Adolf Meyer lecture to the American Psychiatric Association in 1958.

Mayer-Gross's research interests were catholic, and he was a prolific writer: he produced some forty papers during his time in Heidelberg, and seventy while in this country. The quality of these papers was high, and many of them—e.g. his monograph on the oneiroid pattern of experience—have classical importance.

Throughout his career he collaborated happily with colleagues of his own standing and with juniors: among the fruits of this were the widely read and esteemed textbook of psychiatry, first published in 1954; studies of the effects of mescaline and of encephalitis lethargica; and a vademecum for neurologists and psychiatrists examining the mental phenomena of cerebral disease. His contributions to Bumke's *Handbuch der Psychiatrie* were on a heroic scale: he wrote singlehanded nearly half the large volume on schizophrenia, and was also the author of the important section on psychopathology of hallucinations in another volume. While at the Maudsley Hospital he was occupied particularly with the psychological disturbances accompanying various forms of physical disease, and with the analysis of apraxia and of depersonalisation. He began to make observations on the effect of therapeutic hypoglycæmia on brain function, which he pursued actively, both clinically and by biochemical methods, at Crichton Royal Hospital: for him hypoglycæmia provided an experimental psychosis lending itself to exact study as did mescaline and lysergic acid diethylamide. The wide scope of his activity and interests during the fifteen years of his work in Dumfries was made clear in the thoughtful review which he gave in his presidential address on clinical research in psychiatry before the Section of Psychiatry of the Royal Society of Medicine.

A. L. writes:

"I first got to know Mayer-Gross in 1928. Even to a foreign postgraduate it became plain after a few months that this busy Dozent was among the most vigorous figures in a clinic full of learned and energetic people—Wilmanns, Gruhle, Homburger, Steiner, Beringer, and in the offing Karl Jaspers and von Weizsäcker. Mayer-Gross had a prominent place in this distinguished group, and justified it to the full by his impressive output of clinical studies and by his masterly presentation of the symptoms, course, and diagnosis of schizophrenia in the 'Heidelberg' volume of the Bumke *Handbuch*. This last was a triumph of knowledge and sustained effort: no-one would now attempt such a prodigious task, or if he attempted it, succeed as Mayer-Gross did. He had then, as always till the very end, a fund of vitality and confidence that denied obstacles, minimised impossibilities, and led him to tackle boldly every investigation that presented itself as an interesting quest to his fresh, resourceful, urgent mind. He had a sense of obligation towards his chosen branch of medicine and, more specifically, towards the young men who entered it and came under his influence: he spared no pains to train them well and to help their careers.. His nature was generous and direct, and entirely free from rancour. He made no secret of his opinions, neither on controversial matters nor on large issues when the occasion called for it: but he made no enemies because his sincerity and good will were always manifest, and he strove so steadily and buoyantly towards worthy ends."

J. A. H., who was closely associated with Professor Mayer-Gross during the last six years of his life, sends a personal tribute:

"Much may be written about his unremitting labours in the teaching and practice of clinical psychiatry, his exceptional productivity in research, and of his other great contributions to psychiatry throughout the world; his many friends will however cherish his memory for his outstanding personal qualities. Here was no cold intellectual. Willy, as he preferred to be called, was blessed by an exceptional constitution, an ebullience of spirit and driving energy, and not least a charm and mischievous humour which twinkled from his eyes until the day before his death. New ideas came to him with astonishing facility and even in old age he remained a visionary with great hopes and plans for the future of psychiatry. He always said that the best ideas came to him while he shaved in the early morning. Intolerant of the inefficient, the insincere, or the trivial, he was a man of great kindness to patients and staff alike. Even when suffering from recurrent angina he never spared himself if he felt something needed to be done or somebody wanted his help or counsel. He had a liking for young people and was never happier than when surrounded by a group of up and coming psychiatrists. He took a great personal interest in the careers of his younger colleagues and many came from far and wide to seek his advice which he gave without hint of interference in their lives. His limited leisure was devoted mainly to his much loved garden, and it gave him much pleasure to give away some exotic vegetable which he had grown. Of one thing we can be sure, he would have no man mourn his passing."

A. M. writes:

"Although I had already met Mayer-Gross, it was only when our common fate brought him, the late Eric Guttmann, and me to the Maudsley Hospital that I came to know him closely. In those now far-away but still unforgettable days, his exuberant vitality, warmth, optimism, and good humour were a great comfort to us. But his was not an easy-going optimism; he was capable of deep and lasting loyalties. Although he was intolerant of weakness, he was generous of help when he met real distress, and this will be remembered in gratitude by many. His hatred of weakness extended to himself. When he recovered from his first coronary attack in December, 1949, he decided to take risks in order to fulfil what he considered his duty, and to live a full life. So it came about that his activities remained practically unimpaired; he undertook long and arduous journeys as consultant for W.H.O. to India, and lectured extensively in the United States, Germany, and Portugal. Eventually he faced death with the same courage: conscious almost to the last, his main concern was for his wife and to reassure her that he was not afraid.

"His interests were many and varied. He read widely, enjoyed music, and, a real connoisseur of food and wines, he loved the company of congenial friends. When visiting London he always managed to fit in a theatre, film, or picture gallery. He also was a skilled gardener and loved the country. But his dominating love was psychiatry. Others will be more competent than I to speak of his work. I only want to say that the very great intelligence he brought to it was not that of an Intellectual. Seeing him attend with infinite care to the plants in his garden which he had wrested from a derelict and poor soil, one could understand the 'biological' working of his mind and why his writings are so natural, original, and convincing."

M. R. writes:

"Intellectual power is often combined with warmth, charm, lovableness, or integrity; a well-proportioned endowment of all such qualities is more rare and the influence of the man so gifted usually endures. Willy Mayer-Gross was a man of this unusual calibre. Unconscionable integrity, infectious warmth, and human kindliness were his most conspicuous qualities, and by them younger men were attracted throughout his life

into his circle and helped to ripen, unfold, and discover themselves. Rarely did any spark of originality elude his vigilance. He was always ready to listen, never guilty of rejecting ' too soon and too severely '. In this lay much of the secret of his success in the creation of happy, thriving, progressive departments wherever he went. A streak of naivety and credulity was prominent, as in all creative men, and the mortality of ideas was high, but many had to die that a few might flower and bear fruit. In controversy he was undeviating and fearless but he argued without acrimony or malice, and his occasional gusts of wrath were as evanescent as they were unexpected. Though he was sceptical all his life about the value of psychoanalysis in the treatment of mental illness, a number of analysts were among his closest friends.

" It was probably at the Crichton Royal that he spent his most happy and creative years in this country. All who enjoyed the hospitality of Maryfields will remember him in his study, genial and relaxed, bubbling over with new ideas, almost hidden behind the mountainous pile of reprints, books, and correspondence from all corners of the globe lying on the desk. The fragrance of the garden he had made and loved blended with the odour of Continental cooking wafted out from the kitchen. His wife's gentle, sensitive pictures filled the walls wherever there was a space between the bookshelves. Looking out on the rolling blue-black Galloway hills in the distance one had a sense of contentment that was unforgettable.

" He was without affectation or gamesmanship, and this explained why he never acquired a more fluent mastery of conversational English, although it is remarkable that a man learning the language in his late 40s could write such vigorous and lucid prose. His learning and culture lay lightly on him and he was incapable of using it as weapon or embellishment. Nor was there any addiction to theorising to cloud his judgment of what was practicable or worth while.

" Three weeks ago I spent an evening with him in Birmingham. It was only a few days after he had left hospital, but he was in buoyant mood, full of plans for his life in Heidelberg. On his desk were letters he had just written about departments of forensic psychiatry in British universities, growing small marrows, the best place to stay in Rome, and mescaline. Several of his erstwhile juniors called or telephoned to report progress from a mental health exhibition, inquiries came from Uffculme or one of the labs. A day or so before his death we joked about his ' fancy-dress ' for June, when he was to have received an honorary D.SC. from the University of Durham.

" At the end, with his wife at his side, he was firm and unswerving as ever. There had been a perfect understanding. The world is much the poorer for the passing of a noble, great, and indomitable man. In the work he did and those he taught and warmed with his friendship he has left a monument that will endure."

Professor Mayer-Gross is survived by his wife and a son, who is engaged in biological research.

LOUIS CONSTANT DANIEL HERMITTE

M.B. Edin., D.T.M. & H.

Dr. L. C. D. Hermitte, formerly lecturer in pathology in the University of Sheffield, died on Jan. 9 at the age of 66 years.

He was born in the Seychelles, where he spent his childhood. In 1913 he came to Scotland and graduated M.B. at Edinburgh University in 1918. After holding house-appointments in Edinburgh and Southampton, he was appointed assistant in the department of pathology of the Edinburgh Royal Infirmary in 1918. He spent several years in general practice at Bourton-on-the-Water, before he took the D.T.M. & H., and in 1921 he proceeded to a post in Moheema, Assam, India. He continued his postgraduate studies at the University of Paris, where he was awarded the diploma of médecin malariologiste in 1926. He then returned to the Seychelles where he remained until 1933, when he was appointed pathologist to the Royal Infirmary, Sheffield, and honorary lecturer in pathology in the university.

A colleague writes:

" Louis Hermitte was held in affectionate regard and respect by countless undergraduates and postgraduates of the Sheffield School. His extensive background of medicine, and in particular of tropical medicine, proved to be of immense value to patients and colleagues alike. He was a talented artist who applied his gift effectively to his chosen specialty. His histological reports were illustrated admirably, and many of his drawings and paintings are in daily use in laboratories at the Royal Infirmary, Sheffield, the hospital which he loved so much and served so well. He would often work far into the night to perfect his illustrations for published work and for his excellent lectures and demonstrations. Louis Hermitte and his wife were a charming and generous couple who were both blessed with a great sense of fun which showed only kindness. No one has ever shown more bravery and fortitude than he did in overcoming many major medical catastrophes which dogged his life and led to his premature retirement".

Dr. Hermitte's wife died a few years ago, and he leaves a son and a daughter.

Appointments

ADAMS, D. P., M.B. Sheff., D.P.H.: deputy M.O.H. and deputy principal school M.O., Stoke-on-Trent.
ANDERSON, D. J. W., M.B. Wales, D.P.H.: assistant M.O., Cardiff.
HENLEY, D. F., M.B. Durh.: assistant M.O.H. (maternity and child welfare and school health service), West Hartlepool.
JONES, P. O., M.B. Cantab., F.R.I.C.: assistant chemical pathologist, St. Bartholomew's Hospital, London.
LEITCH, J. A., M.B. Edin., D.C.H., D.P.H.: deputy M.O.H. and deputy principal school M.O., West Hartlepool.
SMITH, H. C. T., M.B. St. And., D.P.H., D.P.A.: M.O.H., Penrith.

East Anglian Regional Hospital Board:

BREEN, J., M.B. Queensland: surgical registrar, United Norwich Hospitals.
BROWN, ELIZABETH L., M.B. Edin., M.R.C.P.E.: assistant chest physician, Norwich and East Norfolk Chest Clinic and mass radiography service.
GUNASHEELA, M., M.B. Mysore: surgical registrar, West Suffolk General Hospital.
JHAVERI, G. C., M.B. Bombay: registrar in radiology, Norfolk and Norwich Hospital.
PRYCE, J. D., M.D. Lond.: consultant pathologist, Ipswich and East Suffolk area.
THOMAS, C. G. A., B.M. Oxon., M.R.C.P.: consultant bacteriologist, Norfolk and Norwich area.

Manchester Regional Hospital Board:

BEESON, B. B., M.B. Brist., M.R.C.P.E., D.PATH.: consultant pathologist, Lancaster and Kendal and Lancaster Moor hospital group.
KELLY, FRANCIS, M.B. N.U.I., D.P.H., D.M.R.T.: assistant radiotherapist, North and Mid-Cheshire hospital group.
LEAHY, MAIRE M. P., L.R.C.P.I., D.A.: assistant anæsthetist, Bury and Rossendale hospital group.
PENGELLY, C. D. R., M.D. Brist., M.R.C.P.: consultant physician, North and Mid-Cheshire hospital group.
ROUGHEAD, PETER, M.B. Glasg., D.P.H., D.P.M.: consultant psychiatrist, Springfield Hospital, Manchester.
WALKER, LEONARD, M.R.C.S., D.A.: assistant anæsthetist, North and Mid-Cheshire hospital group.
WILSON, H. W., M.B. Manc., M.R.C.O.G.: consultant obstetrician and gynæcologist, Bury and Rossendale hospital group.

Lancashire County Council:

CANTRELL, NORA, T., M.B., D.C.H.: assistant divisional M.O., Kirby.
DUNLOP, MARGOT G., M.B. Glasg.: assistant divisional M.O., Colne.
ELLIS, MAUREEN, M.B.: assistant divisional M.O., Swinton.

Colonial Appointments:

LINSEL, C. A., M.B. Lond., D.C.P.: assistant director of laboratory services, Kenya.
RUTLEDGE, GEORGE, M.B. Belf., F.R.F.P.S.: specialist, maternal and child health, Tanganyika.
SUSMAN, I. A., M.B. Manc.: M.O. (Leprosy), Gambia.

CORRIGENDA: *Pyelonephritis.*—In the article by Dr. M. S. R. Hutt and his colleagues (Feb. 18, p. 351) the name of the second author should have appeared as J. A. Chambers. In the third line of the second column on p. 351 the dose of ' Pyrexal ' should have been given as 0·007 µg. per kg.

Q Fever in Army Personnel.—In the letter by Colonel Foster (Feb. 18, p. 402) the penultimate sentence under the heading Signs and Symptoms should have ended: ". . . although in the series considered they were present in 90% of cases."

Notes and News

A NURSE'S DUTIES

BECAUSE of new techniques, duties outside the scope of traditional nursing practices are being increasingly allocated to the nurse. Concern has been felt by the Royal College of Nursing that these new duties may restrict her traditional personal care of the sick and expose her to possible litigation. After discussions with the British Medical Association, the college has issued a joint statement setting out some guiding principles.[1] An important recommendation is that duties should be allocated by a joint committee of medical and nursing staff in hospitals, the local authority services, and industrial medical services. It is also pointed out that where medical and ancillary staff is not up to strength, extraneous duties are most likely to be inappropriately delegated to nurses.

MORE BUILDING NOTES

THE fifth of the Ministry of Health's *Building Notes* deals with short-stay psychiatric units.[2] As general guidance, it suggests that the short-stay psychiatric beds for an area should be at one district general hospital. A large department should preferably be in a separate building, but where a smaller unit—perhaps 30 beds—is preferred it could be part of the general ward building, though it should be self-contained. Each ward unit should have two 12–15 bed sections with shared ancillary accommodation. A single treatment centre should normally be adequate even where there are several ward units, and day accommodation could also be shared.

Building Note no. 8 gives guidance on the planning of a physiotherapy department for a general hospital.[3]

University of Cambridge

The Sheild professorship of pharmacology, established in 1946 for only one tenure, is due to lapse on the retirement of Prof. E. B. Verney in September, and the council of the senate have recommended that the chair be re-established on a permanent basis.

University of London

The degree of M.D. has been conferred on Mary E. Carter and I. G. Pryce.

University of Sheffield

Dr. J. J. Daly has been appointed lecturer in medicine.

Royal College of Surgeons of England

On Feb. 14 Sir Russell Brock delivered the Hunterian Oration.

At the Hunterian festival dinner Sir Howard Florey, president of the Royal Society, proposed The College and Sir Stanford Cade replied. Prof. Digby Chamberlain proposed The Guests and Lord Evershed, Master of the Rolls, replied. Sir Russell Brock replied to the toast of the Hunterian Orator, proposed by Sir James Paterson Ross.

Royal College of Surgeons in Ireland

At the charter day dinner on Feb. 11 honorary fellowships were conferred on Dr. I. S. Ravdin and Prof. E. P. Fowler. The fellowship was conferred on P. K. Coakley and A. G. Kilcoyne.

College of General Practitioners

Butterworth gold medal.—This award is offered annually for an essay by a member or associate of the college on a subject connected with general practice. The subject of this year's essay is future trends in general practice and next year's will be the evaluation and management of backache in general practice. Further particulars can be had from the college, 41, Cadogan Gardens, London, S.W.3. The closing date for this year's entries is Sept. 30.

1. Duties and Position of the Nurse. 1961. Obtainable from Royal College of Nursing, 1A, Henrietta Place, London, W.1 (6*d*. post free).
2. Hospital Building Note 5. Short Stay Psychiatric Unit. H.M. Stationery Office. 1961. Pp. 8. 1*s*. 3*d*.
3. Hospital Building Note 8. Physiotherapy Department. H.M. Stationery Office. 1961. Pp. 6. 1*s*. 3*d*.

Course in Criminology at Cambridge

The University of Cambridge has established a postgraduate course in criminology to be held at the Institute of Criminology, which will lead to a diploma. The first course will begin in October, 1961.

105 lectures and 90 seminars will be given with particular reference to the development of criminological and penological thought and practice; the methodology of criminological research; the psychological and psychiatric context of criminal conduct; the sociology of crime; the principles of criminal law and procedure; the sentencing process and effectiveness of punishment and other methods of treatment; the non-institutional and institutional treatment of juvenile, young adult, and adult offenders; and the prevention of crime. Students will have opportunities for practical work, during vacations as well as term-time, at penal and psychiatric institutions, probation and aftercare centres, and other agencies for the prevention of crime and the treatment of offenders. The course will be open to those who hold a university degree in any subject, not necessarily in law; and, in exceptional circumstances, other candidates who have made an important contribution in criminology by research or have outstanding practical experience may be considered. The number of admissions in any one year will be limited. Application forms may be had from the secretary of the Institute, 4, Scroope Terrace, Cambridge, and must be returned not later than March 15 for the course beginning in October, 1961.

British Medical Association

On Thursday, March 16, at 5.30 P.M., at B.M.A. House, Tavistock Square, London, W.C.1, Dr. Maurice Partridge will open a lecture-discussion on the antidepressant drugs.

World Congress of Psychiatry

This congress is to be held in Montreal from June 4 to 10. Further particulars may be had from the general secretary of the congress, Allan Memorial Institute, 1025, Pine Avenue West, Montreal 2.

British Congress of Obstetrics and Gynæcology

This congress will be held from July 16 to 18, 1962, in Bristol. Further particulars may be had from the hon. secretaries of the congress, University Department of Obstetrics, Southmead Hospital, Bristol.

Biochemical Society

The 50th anniversary celebrations of this society will take the form of a three-day meeting to be held in London from March 27 to 29. The meeting will include a symposium on structure and synthesis of macromolecules. On March 28 Sir Hans Krebs will give a Hopkins lecture. His subject will be the physiological role of ketone bodies.

Medical Photography

The medical group of the Royal Photographic Society is to hold a debate on Thursday, March 2, at 7.30 P.M., at 16, Princes Gate, London, S.W.7, when the motion will be that "medical photography is a luxury within the National Health Service". Dr. Andrew Sherrington and Mr. Kenneth Moreman will speak for the motion and Sir Denis Browne and Mr. Leonard Beard against it.

Methods and Organisation in General Practice

A symposium and exhibition on this subject, organised by the Cambridge University Medical School and the East Anglian Faculty of the College of General Practitioners, is to be held on Saturday, March 25, in Cambridge. On Sunday, March 26, Dr. F. A. Nash will demonstrate the logoscope, and Dr. A. E. Clark-Kennedy will give a lecture on clinical diagnosis. Further particulars may be had from the secretary of the medical school, Tennis Court Road, Cambridge.

Electronic Instrumentation for Cardiac Surgery

A symposium on this subject is to be held by the medical and biological electronics group of the British Institute of Radio Engineers and the Postgraduate Medical School of London on Monday, March 27, at 2.30 P.M., at the school, Ducane Road, W.12. The chairman of the symposium will be Dr. D. G. Melrose and the speakers will include Dr. J. P. Shillingford, Mr. H. H. Bentall, Mr. L. D. Abrams, and Dr. C. A. F. Joslin.

International Hospital Congress

This congress is to be held from June 5 to 9 in Venice. The theme chosen is the changing role of the hospital in a changing world. Further particulars may be had from the International Hospital Federation, 24, London Bridge Street, London, S.E.1.

Natural Childbirth Trust of Great Britain

Dr. Pierre Vellay, of the Maternité Rothschild of Paris, will give a lecture on Tuesday, March 21, at 6 P.M., at 26, Portland Place, London, W.1. His subject will be the value of psychoprophylactic preparation for childbirth. Free tickets may be had from the Trust, 26, Seymour Street, W.1.

International Conference on Medical Electronics

An international conference on medical electronics, which is to be combined with the annual conference on electrical techniques in medicine and biology, is to be held from July 16 to 21 in New York City. Those wishing to contribute a paper or exhibit may obtain details from the hon. secretary of the society, Dr. A. Nightingale, Physics Laboratory, St. Thomas's Hospital, London, S.E.1.

Dr. Robin Bannerman, research assistant to the Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, has been awarded first prize in the third *Modern Medical Monographs* competition. He will receive an award of $500, and Grune and Stratton, the founders of the competition, will publish his monograph, which is on thalassæmia. Entries for the fourth competition should be submitted by Dec. 31, 1961, to Dr. Irving S. Wright, 450, East 69th Street, New York 21.

The Royal Institute of British Architects has awarded the Alfred Bossom research fellowship for 1961 to Mr. Peter Cowan, DIPL. ARCH., A.R.I.B.A., and Mr. Raymond Moss, DIPL. ARCH., A.R.I.B.A. They are to study the reconstruction of old urban hospitals, and would be grateful if those with first-hand experience of this work would write to them c/o R.I.B.A., 66, Portland Place, London, W.1.

A weekend course on general medical subjects is to be held on March 11 and 12 at Joyce Green Hospital, Dartford, Kent, under the auspices of the British Postgraduate Medical Federation.

Courses for candidates for the D.M.R.D. and D.M.R.T., starting in October, are now being organised by the Faculty of Radiologists. Further particulars may be found in our advertisement columns.

At a meeting of the Medical Electronics Discussion Group on Friday, March 3, at 6 P.M., at the Institute of Electrical Engineers, Savoy Place, London, W.C.2, there will be a discussion on the clinical value of E.E.G. recording and present trends in general purpose E.E.G. recorders. The opening speakers will be Mr. H. B. Morton and Mr. H. R. A. Townsend.

In *Notes for Guidance of Child Guidance Clinics* Dr. J. Wilson Wheeler, children's officer, Mr. W. F. Houghton, education officer, and Dr. J. A. Scott, medical officer of health and principal school medical officer, describe the London County Council's arrangements for special education and residential care of children and set out how these services may be obtained. A list is included of the 9 child-care divisions in which the council's territory is divided, and the name and address of the district care organiser, the area children's officer, and the divisional medical officer in each is given.

Diary of the Week

FEB. 26 TO MARCH 4

Sunday, 26th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. K. G. Rotter: Common Ear, Nose, and Throat Conditions.

Monday, 27th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. I. G. W. Hill: Problems in the Management of Resistant Heart Disease.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Mr. G. D. Jack: Cough.

Tuesday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4.15 P.M. Dr. R. McP. Livingston: Conjoint Twins. (Arnott demonstration.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. D. Evan Bedford, Mr. T. Holmes Sellors, Dr. J. F. Goodwin, Mr. W. P. Cleland: Cardiac Septal Defects.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. A. G. Spencer: Hypertension and Unilateral Renal Disease—Selection of Patients for Surgery.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. J. A. Dudgeon: Virus Infections. (First of two lectures.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute) Dr. Michael Feiwel: Pruritus Vulvæ.

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine.) *Medical Section.* Dr. R. M. Acheson: Problems in the Measurement of the Maturity of the Growing Skeleton.

Wednesday, 1st

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. R. A. Willis: Examination of the Supposed Increase of Bronchial Carcinoma and of the Validity of its Histological Typing.

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Dr. Richard Hunter: English Psychiatric Writings of the 17th and 18th Centuries.
8 P.M. *Surgery.* Mr. W. R. Trotter, Mr. M. J. Lange, Mr. J. E. Piercy, Mr. Hilary Wade: Treatment of Thyrotoxicosis.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Cytodiagnosis.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. L. L. Bromley: Pulmonary Embolism.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Dr. Imrich Friedmann, Dr. D. A. Osborn, Dr. A. L. Jeanes: Clinical Pathological Conference.

MIDLAND MEDICAL SOCIETY
8.30 P.M. (Birmingham Medical Institute, 36, Harborne Road, Birmingham, 15.) Mr. W. J. Dempster: Anuria following the Transplantation of Kidneys.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. Joint meeting with the Liverpool Medical Institution in Manchester. Dr. A. J. Robertson: Pneumoconiosis due to Tin Oxide. Dr. F. P. Hudson: Dumb Blonde is my Baby, being the Story of Phenylketonuria in Liverpool.

Thursday, 2nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5.30 P.M. Prof. L. P. Garrod: Principles of Antibiotic Therapy in Surgery.

ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Mr. J. M. Small, Dr. J. D. Spillane, Mr. K. I. Nissen: Pain in the Upper Limb.

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5 P.M. Dr. W. J. Whelan: Chemistry and Biochemistry of Glycogen and Starch. (Second of two lectures.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. J. D. N. Nabarro: Oral Hypoglycæmic Agents.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School) Prof. A. L. Hodgkin: Conduction of the Nervous Impulse. (First of two Sherrington lectures.)

UNIVERSITY OF ST. ANDREWS
5 P.M. (Department of Physiology, Queen's College, Dundee.) Mr. John Charnley: Lubrication of Animal Joints in Relation to Orthopædic Surgery.

Friday, 3rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. B. H. Page: Prostatic Surgery.
4 P.M. Dr. F. S. Cooksey: Management of Disability.

ROYAL SOCIETY OF MEDICINE
2.30 P.M. *Laryngology.* Mr. J. I. Munro Black, Prof. S. D. M. Court, Mr. James Crooks: Chronic Sinusitis in Children.
5.30 P.M. *Anæsthetics.* Dr. E. R. Lester, Dr. M. R. Mann, Dr. J. N. Pattinson, Dr. R. W. Emanuel: Angiocardiography.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. S. E. Birdsall: Malignant Diseases of the Larynx.

JAMES YEARSLEY LECTURE
5 P.M. (1, Wimpole Street, W.1.) Mr. J. D. K. Dawes (on behalf of Dr. Louis Verhoeven): Examination of a Chronic Ear.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School.) Professor Hodgkin: Conduction of the Nervous Impulse. (Second of two Sherrington lectures.)

Saturday, 4th

SHEFFIELD REGIONAL PSYCHIATRIC ASSOCIATION
11 A.M. (Mapperley Hospital, Nottingham.) Prof. G. M. Carstairs: Epidemiology of Mental Disorders—its Scope and its Methods.

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